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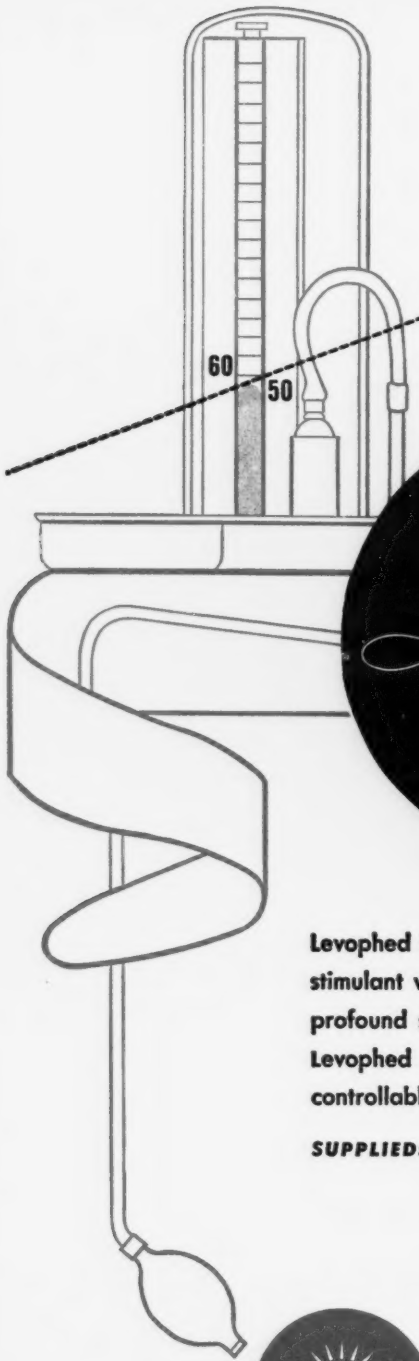

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A Study of the Usefulness and Limitations of Electrical Countershock, Cardiac Massage, Epinephrine and Procaine in Cardiac Resuscitation from Ventricular Fibrillation

By René Wégria, M.D., Charles W. Frank, M.D., Hsueh-Hwa Wang, M.D., George Misrahy, M.D., Robert Miller, M.D., and Peter Kornfeld, M.D.

The efficacy of electrical countershock, cardiac massage, epinephrine and procaine in stopping ventricular fibrillation and restoring a competent ventricular contraction was studied in anesthetized dogs. It was found that countershock is a reliable means of stopping fibrillation. However, it must be preceded by cardiac massage if not applied promptly after the initiation of fibrillation. Epinephrine helps restore a competent ventricular contraction once fibrillation has been stopped by countershock, but it increases the incidence of recurrence of fibrillation. The doses of procaine which constitute a reliable means of stopping fibrillation depress the rhythmicity of the heart to such an extent that the cessation of fibrillation is followed by prolonged periods of cardiac standstill.

VENTRICULAR fibrillation is a cardiac mechanism in which, because of the lack of coordination in the activity of the ventricular fibers, no blood is expelled from the heart and this results in generalized anoxia and death. Fibrillation can be caused by coronary occlusion, electrocution, various drugs or combination of drugs such as digitalis and digitalis-like drugs, chloroform, chloroform-adrenalin, benzol-adrenalin and cyclopropane-adrenalin. The fibrillation induced by digitalis and digitalis-like drugs is of a somewhat particular type however. Ventricular fibrillation can also be initiated by mechanical, chemical or thermal trauma to the heart. Isolated instances have been noted during various surgical procedures, especially those involving the thorax and the heart. It may also occur as an agonal event. Although in certain species of mammals, such as the cat, ventricular fibrillation may stop spontaneously and a normal cardiac mechanism be resumed, in dogs as well as humans the usual type of true fibrillation is essentially a cardiac mechanism which is not spontaneously reversible. It usually persists for as much as 30 minutes until terminal cardiac arrest ensues. It can be stopped, however, when it is not induced by an organic lesion of the myocardium such as myocardial infarction.* The present study was undertaken in an attempt to estimate the respective usefulness and limitations of several procedures and drugs which have been recommended to stop ventricular fibrillation and restore a competent ventricular contraction.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.

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* For a review of the subject of ventricular fibrillation, see references 1 and 2.

Electrical countershock, cardiac massage, epinephrine and procaine were studied.

Methods

Seventy-five dogs weighing between 6 and 31 Kg., 53 of which weighed between 9 and 15 Kg., were anesthetized by the intravenous administration of 25 mg. of sodium pentobarbital per kilogram of body weight. The chest was opened by a midsternal incision, and under artificial respiration the heart was suspended in a pericardial cradle. The mean arterial blood pressu was recorded optically from a cannulated carotid artery. Ventricular fibrillation was induced electrically with an alternating current stimulus of minimal intensity applied through two fishhook electrodes hooked into a gauze pledget soaked with isotonic sodium chloride solution and resting on the left ventricle. Electrocardiograms in the three standard limb leads were recorded at appropriate times.

Cardiac massage consisted of rhythmic compressions of both ventricles with one hand at a rate ranging from 40 to 60 per minute. The descending aorta was compressed and partially constricted during massage to force more blood into the coronary and cerebral circulations. There were marked variations in the arterial pressure reached during massage, the mean pressure ranging between 50 and 100 mm. of mercury.

The technic used to apply electrical countershock in order to stop ventricular fibrillation was essentially that used by Wiggers and Wégria.[1-5] It consisted in enclosing the whole ventricular mass between two copper electrodes padded with cotton soaked with isotonic sodium chloride solution and sending through the heart short bursts, estimated to last about 0.1 second, of a 60 cycle per second alternating current of 110 volts, passing through a variable resistance. Sometimes one such shock was effective and sometimes a series of shocks had to be applied. During all the different procedures used for resuscitation, artificial respiration was maintained, whether cardiac massage was applied or not.

Results

I. Electrical Countershock

A. Countershock Applied after 30 Seconds of Fibrillation. In five dogs, countershock was applied about 30 seconds after the initiation of ventricular fibrillation. A typical experiment is pictured in figure 1. As can be seen in figure 1, the control arterial blood pressure was 110 mm. Hg. Before electrical stimulation resulted in ventricular fibrillation, two electrical stimuli were unsuccessful in inducing ventricular fibrillation but resulted in two short episodes of ventricular tachycardia accompanied by a temporary drop of the arterial blood pressure. At the first arrow, a third electrical stimulus resulted in ventricular fibrillation. The arterial blood pressure promptly fell toward zero. Abou

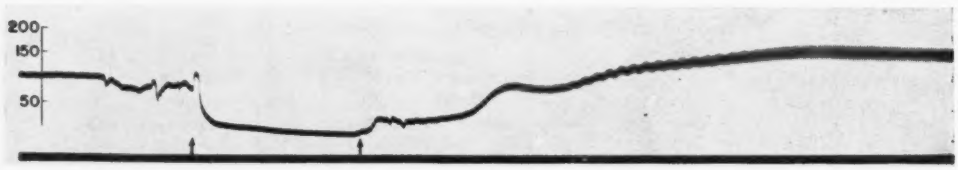

Fig. 1. Mean arterial blood pressure before, during and after a bout of ventricular fibrillation lasting 38 seconds. At first arrow, induction of ventricular fibrillation; at second arrow, electrical countershock resulting in cessation of ventricular fibrillation and resumption of regular sinus rhythm. At the left of the tracing, blood pressure scale in mm. Hg. Time in seconds.

one-half minute after the induction of ventricular fibrillation, two countershocks stopped ventricular fibrillation and regular sinus rhythm was resumed. The arterial blood pressure rose progressively and reached a maximum of 165 mm. Hg, 2 minutes and 20 seconds after the initiation of fibrillation. In a part of the record not reproduced in figure 1, the blood pressure was seen to decrease progressively from its peak of 165 mm. Hg to values of 105, 98, 87 and 50 mm. Hg 15, 25, 45 and 60 minutes, respectively, after the initiation of fibrillation. In figure 2 are reproduced electrocardiographic tracings (lead II) recorded during the same experiment. Section *A* is the control electrocardiogram showing regular sinus rhythm. Section *B* was taken at the end of the period of ventricular fibrillation. The record of section *C*, taken one minute after the initiation of

fibrillation, that is, 22 seconds after fibrillation had been stopped, demonstrates that regular sinus rhythm had been resumed. The S-T segment of the electrocardiogram was markedly elevated. Section *D*, recorded seven minutes after the initiation of fibrillation, shows that the electrocardiogram had resumed its control form. Essentially similar observations were made in all five experiments of this type. Countershock was effective in stopping fibrillation in all five dogs. Immediately thereafter, the ventricles began to beat spontaneously. In three dogs regular sinus rhythm was resumed immediately; in the other two dogs, auricular fibrillation lasting 10 and 90 seconds, respectively, preceded the resumption of regular sinus rhythm. It is believed that these bouts of atrial fibrillation were induced by the electrical countershocks which stopped the fibrillation in the ventricles. In all five dogs, the blood pressure rose rapidly to or above control as soon as ventricular fibrillation was stopped. In three, the blood pressure remained above 100 mm. Hg for one hour; in the fourth dog the blood pressure was 80 mm. Hg during the control period, and was 80, 77, 68 and 70 mm. Hg, respectively, 5, 15, 40 and 60 minutes after the initiation of fibrillation. The fifth dog is the one described in figure 1. Electrocardiograms were recorded in four of the five experiments. In three of these there was marked displacement of the S-T segment immediately after the re-establishment of a coordinated ventricular beat. This displacement disappeared within three minutes.

B. Countershock Applied after Five Minutes of Fibrillation. In four dogs countershock was applied five minutes after the initiation of ventricular fibrillation. During the five minutes of fibrillation, the character of the fibrillation changed markedly. Direct observation of the ventricles revealed that the initial fine, rapid quivering became progressively coarser and slower. A similar evolution in the fibrillatory process can be seen on the electrocardiogram of such an experiment, reproduced in figure 3. *A*, the control electrocardiogram, shows the cardiac mechanism to be regular sinus rhythm. Between *A* and *B*, ventricular fibrillation was induced. Sections *B*, *C* and *D*, recorded after 20 seconds, 1½ minutes and 4½ minutes of fibrillation, respectively, illustrate that the rate of fibrillation slowed from about 450 per minute to approximately 300 per minute. Between *D* and *E*, electrical countershock was applied after five minutes of ventricular fibrillation. It was effective in stopping ventricular fibrillation. Section *E*, recorded 20 seconds after the countershock, shows regular sinus rhythm with an atrial rate of 55 per minute and ventricular standstill. Section *F* recorded seven minutes later illustrates that the sinus rhythm was still present and a slow idioventricular rhythm of about 25 per minute with very abnormal QRS complexes had appeared. Complete atrioventricular block was present.

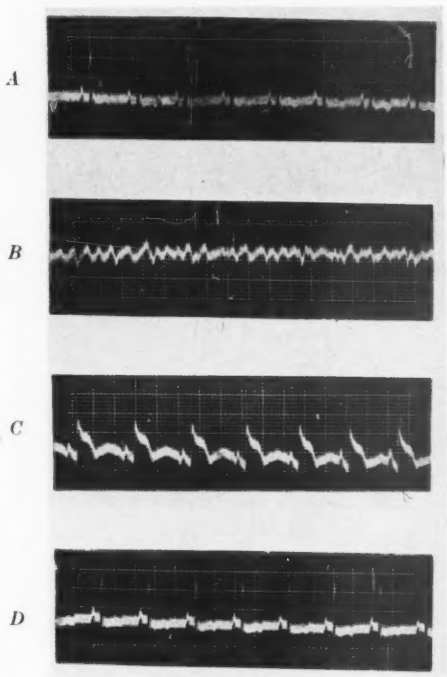

FIG. 2. Sections of electrocardiogram, lead II, recorded during the experiment of figure 1; *A*, during the control period; *B*, at the end of the period of fibrillation; *C*, one minute and *D*, seven minutes after the initiation of fibrillation.

In all four dogs similar observations were

made: ventricular fibrillation was stopped by electrical countershock; sinus rhythm was resumed, first with ventricular standstill then with idioventricular rhythm. Such ventricular beats were ineffective in raising the arterial blood pressure. During the 10 to 20 minute period of observation which followed the cessation of ventricular fibrillation, the heart deteriorated further and the ventricular rate remained very low.

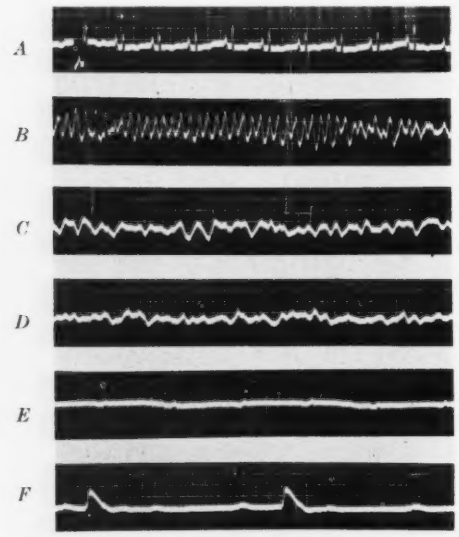

FIG. 3. Electrocardiogram, lead II, before, during and after a bout of ventricular fibrillation lasting 5 minutes. *A*, control tracing; *B*, tracing after 20 seconds of fibrillation; *C*, tracing after one and one-half minutes, and *D*, tracing after four and one-half minutes of fibrillation. Between *D* and *E*, electrical countershock was applied after five minutes of fibrillation. *E*, electrocardiogram taken 20 seconds after electrical countershock, showing regular sinus rhythm and ventricular standstill; *F*, tracing recorded seven minutes after *E*, showing regular sinus rhythm, complete atrioventricular block and idioventricular rhythm with very abnormal QRS complexes.

II. Cardiac Massage

As will be shown by the observations reported in section III, cardiac massage alone did not stop ventricular fibrillation. However, it prevented the progression of the fibrillatory process from the early fine, fast type to the late, slow, coarse type. Massage even caused the late type to revert to the early type at least within the limits of time which were studied.

III. Cardiac Massage and Electrical Countershock

A. Cardiac Massage–Electrical Countershock Repeatedly Applied after Five Minutes of Fibrillation. In a group of five dogs, ventricular fibrillation was induced and observed for five minutes. Phenomena similar to those described in section I, part B were observed. After this five-minute period of fibrillation, cardiac massage was instituted for 30 seconds. Massage was seen to change the fibrillation from the late type (slow and coarse) to the early type (rapid and fine). It was also noted that under the influence of massage the ventricles which first felt flabby to the massaging hand became rather suddenly much firmer. After the 30 seconds of massage, electrical countershock was applied and stopped ventricular fibrillation in all experiments. In this group also, the ventricular contractions were ineffective in raising the blood pressure. When it became apparent that the ventricular contraction was going to deteriorate further, massage was administered again although the danger of inducing ventricular arrhythmias by massaging ventricles contracting in a coordinated manner was fully realized. Indeed, massage resulted in ventricular fibrillation in all five dogs. This sequence of maneuvers (massage resulting in ventricular fibrillation followed by countershock stopping fibrillation) was repeated from two to five times in each of these five dogs. The maneuver, massage-countershock, was stopped when it was noted that the ventricles were beginning to beat more vigorously and the arterial blood pressure was rising. At this time the blood pressure rose above control level in four of the five dogs. In one of these four dogs it remained above 100 mm. Hg for one hour and in the other three it ranged between 60 and 80 mm. Hg. In the fifth dog, the blood pressure remained around 50 mm. Hg. In four of the five dogs electrocardiographic changes were slight, consisting of some S-T deviation, T-wave changes or both. These changes persisted throughout the period of observation but tended to decrease. In the

remaining dog, the changes in the S-T segment were marked, but tended to decrease also.

B. Countershock Applied after 9 to 18 Minutes of Fibrillation during which the Ventricles Were Massaged Intermittently. In five dogs countershock was applied after ventricular fibrillation had persisted for 9 to 18 minutes. During fibrillation, cardiac massage was administered continuously for 7 to 10 minutes except for interruptions of about 30 seconds every one to two minutes to allow the recording of electrocardiograms. After this period of 7 to 10 minutes, massage was discontinued for one and one-fourth to three minutes and in only one dog for four and three-fourths minutes, then the massage-countershock procedure was instituted. In all dogs, fibrillation was stopped by the countershock, and coordinated ventricular beats were restored. The arterial blood pressure rose rapidly within the control range of about 100 mm. Hg. In the dog in which fibrillation was allowed to persist for 18 minutes and no massage given for four and three-fourths minutes, the blood pressure did not rise above 75 mm. Hg; the control blood pressure of this dog was 90 mm. Hg. Figure 4 illustrates the electrocardiograms recorded during one of these experiments. Section *A* recorded during the control period shows regular sinus rhythm. Section *B* reveals that after seven minutes of fibrillation during which cardiac massage had been applied, fibrillation was still of the early type, but as seen in section *C*, it became slow two minutes after massage had been discontinued. Section *D* illustrates that fibrillation regained the characteristics of the early type of fibrillation after massage. Section *E* is the tracing after fibrillation had been stopped, regular sinus rhythm restored and the heart allowed to recover so that the electrocardiogram was similar to the control tracing. Electrocardiograms were recorded on four of the five dogs after ventricular fibrillation had been stopped. None was recorded on the dog in which no massage was given for the longest time. The electrocardiographic changes were essentially similar to those described in the group of experiments in which countershock was applied after 30 seconds of fibrillation (paragraph I, part A) and they evolved similarly.

IV. Epinephrine

The effect of epinephrine alone on ventricular fibrillation was studied in four dogs. Ventricular fibrillation was induced electrically as previously described and after a period of at least 30 seconds of fibrillation, 0.05 mg. of synthetic l-epinephrine per kilogram of body weight was injected, half of the amount in each ventricular cavity. The total amount of the drug given was dissolved in 1 cc. of a 0.9 per cent sodium

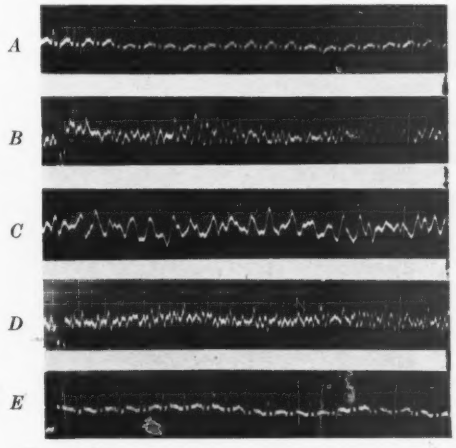

FIG. 4. Electrocardiogram, lead II, before, during and after a bout of ventricular fibrillation. *A*, control tracing; *B*, tracing after seven minutes of fibrillation, cardiac massage having been applied except for interruptions to allow recording of the electrocardiogram; *C*, tracing after nine minutes of fibrillation and two minutes after last massage; *D*, tracing after 10 minutes of fibrillation and immediately after massage; *E*, tracing 20 minutes after inception of fibrillation and 10 minutes after electrical countershock had stopped fibrillation.

chloride solution. To be sure to submit the ventricles to the effect of the drug, after the injection the ventricles were massaged 10 times within about one-half minute, the descending aorta being partially occluded with the fingers. After this last maneuver, the effects of the drug were observed without any further interference. In none of the four experiments was it observed that epinephrine stopped fibrillation. However, the drug modified the fibrillatory process. Fibrillation became very fine and rapid and remained so for some time. Figure 5 illustrates the electrocardiogram of such an experi-

ment. The record of section *A* shows ventricular fibrillation after 30 seconds of fibrillation. The tracing in section *B*, recorded 3 minutes and 40 seconds after the administration of epinephrine, that is five minutes after the initiation of fibrillation, shows that the fibrillation was still very rapid and fine; this is very striking when this tracing is compared with the tracing of figure 3, section *C*, which shows how much coarser and slower fibrillation had become after 1 minute and 30 seconds when not modified by epinephrine. The record of section *C* in figure 5 shows that even after 11 minutes and 30 seconds of fibrillation, that is, 10 minutes and 10 seconds after the administration of epinephrine, the fibrillation was still

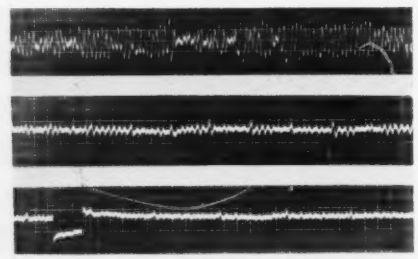

FIG. 5. Electrocardiogram, lead II, showing ventricular fibrillation: In section *A* after 30 seconds of fibrillation, in section *B* after five minutes of fibrillation and 3 minutes and 40 seconds after the administration of epinephrine, in section *C*, after 11 minutes and 30 seconds of fibrillation and 10 minutes and 10 seconds after the administration of epinephrine.

very fine and rapid, and this is especially striking when the tracing of figure 5, section *C* is compared with the tracing of figure 3, section *C*.

In these four experiments the control arterial blood pressures were 125, 110, 160 and 160 mm. Hg, respectively. Massage-countershock was applied respectively 9½, 16, 11 and 10½ minutes after the injection of epinephrine. Ventricular fibrillation was stopped and a coordinated ventricular beat restored. However, because of the recurrence of ventricular fibrillation, massage-countershock had to be used five and six times, respectively, in the first two experiments. The highest arterial blood pressures reached were 135, 135, 130 and 195 mm. Hg, respectively. At the time the observation was discontinued, that is, 24, 23, 19, and 17 minutes after the injection of epinephrine, the blood pressures were 65, 70, 130 and 40 mm. Hg, respectively.

V. Procaine

To study the effect of procaine on ventricular fibrillation a technic essentially similar to that used for the study of epinephrine was employed. Ventricular fibrillation was induced electrically as previously described; then after 30 seconds of fibrillation, variable amounts of a 20 per cent solution of procaine hydrochloride were injected, half into each ventricular cavity. This was followed by 10 massages of the ventricles given within one-half minute and with the aorta partially occluded. After the massage the heart was observed.

A. Dose of 200 mg. of Procaine Hydrochloride per Kilogram of Body Weight. In all four dogs which received this dose of procaine, ventricular standstill occurred during or immediately following massage. One of these experiments is illustrated by figure 6. Two dogs remained in ventricular standstill for the 10 minutes and 30 seconds and 14 minutes and 40 seconds following the injection of procaine that they were observed. In the other two dogs, five and seven minutes, respectively, after the inception of fibrillation ventricular standstill was followed by slow, localized, irregular ventricular contractions which did not raise the arterial blood pressure. The electrocardiographic deflections corresponding to those ventricular contractions were continuous, slow, irregular undulations very variable in size and form, essentially similar to those seen in the late type of fibrillation previously described. After a period of 10 to 20 minutes of observation, all four hearts were massaged whether they were in ventricular standstill or in what will be referred to from now on as coarse ventricular fibrillation. All four dogs remained in or developed ventricular fibrillation. In three of the four dogs, 1 mg. of epinephrine injected into the ventricles at this time increased the frequency of the fibrillatory waves.

B. Dose of 150 mg. of Procaine Hydrochloride per Kilogram of Body Weight. In all of seven dogs this dose of procaine produced a slowing

and coarsening of the ventricular fibrillation from a frequency of 600 to 800 per minute to a frequency of 80 to 150 per minute. In four of the seven dogs, coarse fibrillation was followed by ventricular standstill in one to three minutes after the administration of procaine. All four dogs remained in ventricular standstill for a 10 to 15 minute period of observation, after which cardiac massage and 1 mg. of epinephrine resulted in coarse ventricular fibrillation. In the other three dogs, procaine made the fibrillation coarser and slower without producing ventricular standstill. After a period of observation of 10 to 15 minutes, cardiac massage alone in one of the three dogs and cardiac massage–epinephrine in the other two modified the character of the fibrillation without stopping it.

D. Dose of 50 mg. of Procaine Hydrochloride per Kilogram of Body Weight. At this dosage, procaine slowed fibrillation from a frequency of 550 to 850 per minute to 250 to 450 per minute and fibrillation persisted for a 10 minute period of observation in four out of six dogs. In the fifth dog, ventricular fibrillation slowed, then was followed by ventricular standstill seven minutes after the inception of fibrillation. Then the electrocardiographic deflections were so constant in shape and frequency that this cardiac mechanism may be called ventricular flutter. The frequency of the flutter waves was between 95 and 140 per minute. After three to four minutes of ventricular flutter, slow fibrillation returned and persisted for a 10 to 15 minute period of observation.

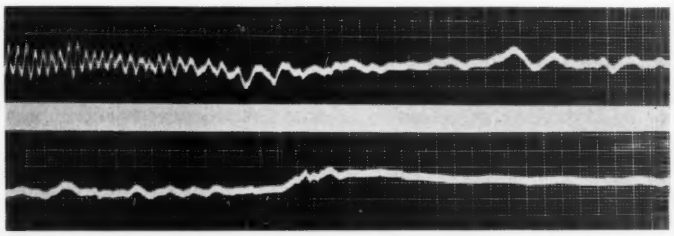

FIG. 6. Continuous electrocardiographic tracing, lead II, showing ventricular fibrillation becoming coarser and slower and then ending in ventricular standstill after the intracardiac administration of 200 mg. of procaine per kilogram of body weight and cardiac massage. Procaine was administered 30 seconds after the initiation of fibrillation and the recording of the tracing was begun immediately after the injection of procaine.

C. Dose of 100 mg. of Procaine Hydrochloride per Kilogram of Body Weight. With a dose of 100 mg. of procaine per kilogram, results essentially similar to those observed with the dose of 150 mg. per kilogram were observed in a group of seven dogs. Three of these seven dogs went into ventricular standstill during or immediately following massage. One of the three reverted to slow ventricular fibrillation after 30 seconds of ventricular standstill. Massage did not stop ventricular fibrillation. The other two remained in standstill for a 10-minute period of observation after which cardiac massage resulted in ventricular fibrillation. In the other four dogs, procaine slowed fibrillation considerably from a frequency of 600 to 850 to a frequency of 100 to 250 per minute, and all four hearts went through a period during which regular sinus rhythm of a rate of 30 per minute with prolonged atrioventricular conduction and intraventricular block developed. These ventricular contractions did not raise the aortic blood pressure. As the heart did not seem to improve dynamically after three minutes of sinus bradycardia, the ventricles were massaged, which resulted in ventricular fibrillation. Massage-countershock was instituted 20 minutes after the beginning of the first bout of fibrillation and restored regular sinus rhythm. At this time 1 mg. of epinephrine resulted in sinus tachycardia and the arterial blood pressure reached 220 mm. Hg. The preparation was not followed any further.

In the sixth dog, procaine slowed fibrillation; then ventricular flutter of a rate of 330 per minute was observed. Four minutes after the

inception of fibrillation, ventricular flutter of a rate of 85 per minute was present and three minutes later ventricular standstill occurred. It persisted for four minutes, then irregular, coordinated ventricular beats were resumed, at which time the atria were noted to beat infrequently and irregularly; the ventricular contractions were idioventricular in origin. As the ventricular beats did not raise the arterial blood pressure, cardiac massage was administered for one and one-half minutes, which resulted in sinus tachycardia with prolonged atrioventricular conduction. The arterial blood pressure rose progressively, reaching a peak of 130 mm. Hg 17 minutes after the inception of the first bout of ventricular fibrillation, then it declined progressively and was 70 mm. Hg one hour after the initiation of fibrillation; the control blood pressure was 120 mm. Hg. The electrocardiogram was similar to the control tracing 16 minutes after the beginning of ventricular fibrillation.

E. Dose of 20 mg. of Procaine Hydrochloride per Kilogram of Body Weight. In all eight dogs which received this dose, ventricular fibrillation became coarser and slowed from a rate of 500 to 750 per minute to a rate of 150 to 400 per minute. In three of these dogs, fibrillation persisted for a 10, 12 and 16 minute period of observation, after which massage-countershock resulted in the return of a regular coordinated ventricular beat. However, the arterial blood pressure in all three dogs either did not rise, or rose but then decreased within approximately five minutes to levels of 30 to 50 mm. Hg. In the remaining five dogs, ventricular standstill occurred 6, 8½, 9½, 10 and 14 minutes, respectively, after the inception of fibrillation. The dog which developed standstill after nine and one-half minutes remained in ventricular standstill for six minutes at which time massage resulted in ventricular fibrillation. Massage-countershock restored a coordinated ventricular beat and the blood pressure reached a peak of 120 mm. Hg, but it declined to 20 mm. within five minutes. In the other four dogs, ventricular standstill was immediately followed by a slow idioventricular rhythm of from 10 to 50 beats per minute in three dogs and regular sinus rhythm with a 4:1 atrioventricular block in the other dog. These coordinated beats were weak and unable to raise the aortic blood pressure. Cardiac massage at this time resulted in ventricular fibrillation. Massage-electric countershock caused the resumption of regular sinus rhythm in all four dogs. In three dogs the blood pressure rose and remained above 90 mm. Hg and was still 90 mm. Hg or more 45 to 60 minutes after the initiation of fibrillation. In the fourth dog in which ventricular fibrillation persisted for 14 minutes, the blood pressure rose to 75 mm. Hg but decreased markedly within a few minutes.

VI. Procaine and Continuous Massage for Ten Minutes

Because it was thought that procaine might be more effective in stopping ventricular fibrillation and restoring a competent ventricular contraction if myocardial anoxia were prevented, a series of experiments was conducted in which cardiac massage was continued for 10 minutes after the injection of procaine into the ventricles. Under such circumstances, a dose of 50 mg. of procaine hydrochloride per kilogram of body weight immediately slowed the fibrillation from a rate of 500 to 650 to a rate of 250 to 300 per minute, and the fibrillation became slower and coarser. However, it persisted continuously in three of the five dogs; in the other two dogs there was a brief period of ventricular standstill lasting 30 and 60 seconds, one and one-half minutes after the injection of procaine. These episodes of ventricular standstill were followed by the resumption of ventricular fibrillation on continuing cardiac massage. After 10 minutes of massage, ventricular fibrillation was stopped with the electrical countershock in all five dogs and regular sinus rhythm with coordinated ventricular beats was resumed. One-half hour after the initiation of fibrillation, that is, 20 minutes after fibrillation had been stopped by countershock, the mean arterial blood pressures in the five dogs were 60, 75, 20, 40 and 20 mm. Hg, respectively, their control blood pressures being 135, 110, 120, 80 and 105 mm. Hg, respectively. In another five dogs, a dose of 20 mg. of procaine per kilogram and continuous massage for 10 minutes, resulted in a gradual slowing of the

fibrillation from a rate of 600 to 700 to a rate of 300 to 400 per minute, but fibrillation persisted in all five dogs. After the 10 minute period of massage, massage-countershock resulted in the resumption of regular sinus rhythm. In three dogs the blood pressure rose to 170 to 180 mm. Hg and was still 75 to 85 mm. Hg 30 minutes later. In the other two dogs, the blood pressure rose only slightly when fibrillation was stopped and fell to around 40 mm. of mercury within 5 minutes.

VII. Epinephrine and Countershock after Five Minutes of Fibrillation

It has been reported in previous paragraphs that, when electrical countershock was applied after fibrillation had been allowed to evolve spontaneously for approximately five minutes, electrical countershock still stopped ventricular fibrillation, but the effect of the ischemia due to the five-minute period of fibrillation was such that the ventricular contractions, although coordinated, were ineffective in raising the aortic blood pressure, and the intracardiac conduction (atrioventricular and intraventricular) as well as the rhythmicity of the ventricles was much depressed. Cardiac massage under such circumstances was shown to improve the dynamics of the ventricles as well as the intracardiac conduction and the rhythmicity of the ventricles. However, when, under the circumstances of these experiments, massage was applied to ventricles beating weakly but in a coordinated manner, it frequently resulted in the inception of ventricular fibrillation. It was thought of interest to investigate whether, by injecting epinephrine into the ventricular cavity just prior to applying the electrical countershock, it might not be possible to avoid massage and thereby the return of ventricular fibrillation and yet to obtain immediately upon stopping fibrillation with the electrical countershock coordinated ventricular contractions strong enough and frequent enough to restore an adequate circulation without any appreciable latent period. For this purpose ventricular fibrillation was induced electrically in 10 dogs. In 3 of these 10 dogs 0.05 mg. of epinephrine per kilogram of body weight was injected, half of the amount in each ventricular cavity after five minutes of fibrillation. In the other seven dogs, 0.01 mg. of epinephrine per kilogram of weight was similarly injected after five minutes of fibrillation. The total amount of the drug given was dissolved in 1 cc. of a 0.9 per cent sodium chloride solution. After the injection of epinephrine into the ventricles, the ventricles were massaged 10 times over a 30-second period; then electrical countershock was applied.

The first one of the three dogs which received 0.05 mg. of epinephrine per kilogram of body weight had a control blood pressure of 110 mm. Hg. After five minutes of ventricular fibrillation, epinephrine was administered; then ventricular fibrillation was promptly stopped by electrical countershock and a coordinated ventricular contraction immediately supervened. However, within a few seconds spontaneous ventricular fibrillation recurred. It was stopped immediately by countershock and an effective coordinated ventricular beat immediately followed the termination of fibrillation. After a period of 2 minutes and 10 seconds during which an effective ventricular contraction persisted and the blood pressure rose above 160 mm. Hg, ventricular fibrillation again recurred spontaneously. It was stopped by countershock and immediately followed by effective ventricular beats, the blood pressure rising above 160 mm. Hg, but after 20 seconds, ventricular fibrillation recurred once more. It was stopped again promptly by countershock and immediately followed by effective ventricular beats, the blood pressure rising above 160 mm. Hg. The blood pressure was 170, 90, 100, 120, 115, and 100 mm. Hg 10, 15, 20, 30, 45, and 60 minutes, respectively, after the induction of ventricular fibrillation. Twenty minutes after the inception of the initial ventricular fibrillation, the electrocardiogram was similar to the control tracing. The second of the three dogs which received 0.05 mg. of epinephrine per kilogram of weight reacted essentially in a similar manner except for the important fact that ventricular fibrillation recurred spontaneously only once 30 seconds after it had been stopped. In the third and last dog of this series, 10 electrical countershocks over a period of 45 seconds had to be applied before ventricular fibrillation was stopped. Fibrillation was then followed by ven-

tricular standstill, then by weak ventricular contractions. The blood pressure remained around 10 mm. Hg for about two minutes, then it rose as high as 230 mm. Hg, i.e. 70 mm. Hg above the control blood pressure. It then decreased and was 170, 115, 115, 120 and 140 mm. Hg 10, 20, 30, 40 and 60 minutes, respectively, after the inception of the initial bout of ventricular fibrillation. Because of the frequent recurrence of ventricular fibrillation in these three dogs, similar experiments were conducted with a smaller dose of epinephrine.

In seven dogs, ventricular fibrillation once induced was allowed to evolve for five minutes, at which time 0.01 mg. of epinephrine per kilogram of body weight was injected into the ventricles. The ventricles were then massaged 10 times and electrical countershock applied. In two of these seven dogs, although ventricular fibrillation was stopped by the countershock, 10 and 19 countershocks were necessary. The ventricular beats never were strong enough to raise the arterial blood pressure significantly. In the other five dogs, ventricular fibrillation was stopped by the countershock, but, within a few seconds to two and one-half minutes after the first countershock, it recurred once in four of the five dogs and twice in the fifth dog. Every time countershock was used successfully to stop ventricular fibrillation. After fibrillation was stopped, the blood pressure rose above its control level then decreased progressively. In these five dogs the control mean arterial blood pressures were 180, 180, 130, 115 and 150 mm. Hg, and one hour after the initiation of fibrillation pressures had progressively decreased to 120, 140, 85, 80 and 110 mm. Hg.

Discussion

From our observations as well as those of others,[1-6] it is clear that electrical countershock when applied to the ventricles of dogs which have been fibrillating for about 30 seconds was very effective in stopping electrically induced ventricular fibrillation. A few seconds after the termination of ventricular fibrillation, regular sinus rhythm was resumed, this being sometimes preceded by an episode of atrial fibrillation induced by the countershock. The mean arterial blood pressure promptly rose above control, then progressively decreased to approximately its control level. It might then progressively decline over the next hour; this might occur even without a period of ventricular fibrillation in dogs with open chest. The electrocardiogram returned to its control form soon after the ventricular fibrillation had been stopped. If the ventricles were allowed to fibrillate for five minutes, fibrillation was seen on direct observation of the heart to become coarser and slower and the electrocardiographic tracing revealed that the rate of the fibrillation became progressively slower. Electrical countershock applied after five minutes of fibrillation still stopped fibrillation, but the myocardium had been so damaged during this five minute period of fibrillation that atrioventricular block and temporary ventricular standstill were observed. The ventricular contractions remained ineffective in raising the arterial blood pressure, and the heart progressively deteriorated further as previously observed by Dow and Wiggers.[6] Manual massage of the ventricles alone was never observed to stop ventricular fibrillation, which is in agreement with the findings of Stearns, Maison and Stutzman.[7] However it ensured a good enough coronary circulation to prevent the fibrillatory process from deteriorating from the early fine, fast type to the late, coarse and slow type, and it even made the late type revert to the early type. When, after the ventricles had been allowed to fibrillate for five minutes, the ventricles were massaged for 30 seconds, cardiac massage of even such a short duration changed the character of the fibrillation. The fibrillation which had become of the late type, slow and coarse, by the end of the five minute period of fibrillation reverted to the early type, fine and rapid. Electrical countershock applied after five and one-half minutes of fibrillation, cardiac massage being applied for the last 30 seconds, stopped fibrillation, but the ventricular contractions were weak and did not seem to improve. When it seemed probable that the ventricular contraction would not improve but rather deteriorate further, the ventricles were again massaged although it was realized that massage of the ventricles beating in a coordinated manner would probably induce ventricular arrhythmias

and possibly ventricular fibrillation.* Indeed, fibrillation was induced. It was then stopped with the electrical countershock. This countershock-massage-countershock maneuver was repeated two to five times in each of the dogs of this series. During massage of the fibrillating ventricles, the ventricular mass which first felt very flabby to the massaging hand, rather suddenly became strikingly much firmer. When the ventricles were noted to beat more vigorously and the arterial blood pressure began to rise after fibrillation had been stopped electrically, massage was not administered again. At this time the blood pressure rose above its control level in most of these dogs, but by the end of one hour it had fallen markedly in most dogs. It seems probable that one longer period of massage right after the five minutes of fibrillation would have given the same or better results without the repeated use of countershock.

This was confirmed to a certain extent by the observations made on a group of five dogs in which fibrillation was allowed to persist for 9- to 18-minute periods during which the ventricles were massaged continuously except for interruptions of 30 seconds every one or two minutes to permit the recording of electrocardiograms. At the end of the period of fibrillation no massage was given for one and one-fourth to three minutes and in only one dog for four and three-fourths minutes. Then countershock preceded by a last short period of massage restored regular sinus rhythm, vigorous ventricular contractions and a level of blood pressure within the control range except in the dog in which massage was interrupted for four and three-fourths minutes. In this last dog the blood pressure rose but remained slightly below control level. It is probable that, when the experimental conditions, especially the duration of the bout of ventricular fibrillation, were such that the arterial blood pressure was not restored to control level, the myocardial damage produced played a role, but it is no less probable that damage to other structures such as the vasomotor center might have been an important determinant of the level to which the blood pressure was restored. In short it seemed that ventricular fibrillation, per se, did not produce any damage to the myocardium and/or other structures in the body and that complete recovery from ventricular fibrillation was possible if fibrillation lasted only a few seconds, or if during longer periods of fibrillation an adequate supply of oxygenated blood to the heart and the whole body was maintained. As far as recovery of the heart was concerned, nothing seemed to be gained by trying to stop fibrillation before adequate massage of the ventricles had restored sufficient coronary blood supply for a long enough period. It must be added that when manual massage of the ventricles was applied, often large epicardial hemorrhages appeared after the blood pressure returned to or toward control level. No attempt was made to estimate either the depth of such hemorrhages or their effects on the dynamics of the heart.

In our experiments epinephrine never stopped fibrillation although it modified the fibrillatory process very markedly. It was observed that epinephrine rendered the fibrillation much more rapid and fine and prevented the progressive slowing and coarsening of the fibrillation. Massage-countershock applied after periods of fibrillation ranging between 10 and 16½ minutes from the beginning of the fibrillation stopped the fibrillation and restored coordinated, effective ventricular beats, but the arterial blood pressure, except in one experiment, fell rapidly.

A dose of 200 mg. of procaine hydrochloride per kilogram of body weight stopped ventricular fibrillation within a few seconds, but after fibrillation had been stopped, the ventricles remained in standstill or reverted to a slow type of ventricular fibrillation. Massage and massage-epinephrine resulted in fibrillation. With doses of 100 and 150 mg. of procaine, similar results were observed, except that ventricular standstill occurred less frequently. In those

* In our experience, massage of the ventricles contracting in a coordinated manner, administered as far as possible during diastole, induced ventricular tachycardia lasting as long as the massage and very seldom ventricular fibrillation in normal hearts. In hearts which had been allowed to remain in ventricular fibrillation for five minutes, after which fibrillation had been stopped electrically, massage resulted in ventricular fibrillation in almost all cases.

dogs in which standstill was not obtained, procaine slowed the fibrillation. A dose of 50 mg. of procaine slowed the fibrillation without stopping it in four out of six dogs. In the fifth dog, procaine stopped fibrillation seven minutes after the initiation of fibrillation; the ventricles began to beat, the cardiac mechanism being sinus bradycardia with prolonged atrioventricular conduction time and intraventricular block. Because the ventricular contractions were ineffective in raising the aortic pressure and did not seem to improve dynamically, the ventricles were massaged and ventricular fibrillation resulted. Massage-countershock restored regular sinus rhythm, and with epinephrine the arterial blood pressure rose to a peak of 220 mm. Hg. In the sixth dog, ventricular standstill followed the administration of procaine. It occurred seven minutes after the initiation of fibrillation. The standstill was followed by an idioventricular rhythm. Because of the weakness of the ventricular contractions, massage was resorted to. The heart improved greatly and the blood pressure rose to a peak of 130 mm. Hg to decline to 70 mm. Hg by the end of one hour from the induction of fibrillation. With a dose of 20 mg. of procaine, fibrillation persisted but was made slower in three out of eight dogs. Massage-countershock restored coordinated beats, but the arterial blood pressure did not rise very markedly, or fell to very low levels within a few minutes. In the other five dogs, ventricular standstill occurred rather late, 6 to 14 minutes after the inception of fibrillation. One of these five dogs remained in ventricular standstill; massage induced ventricular fibrillation and countershock-massage restored an efficient ventricular beat, the arterial pressure rising to a peak of 120 mm. Hg but declining rapidly. In the other four dogs, ventricular standstill was followed immediately by regular sinus rhythm or idioventricular rhythm. Because of the weakness of the ventricular contraction, massage was applied. It induced ventricular fibrillation. Massage-countershock restored regular sinus rhythm with adequate arterial blood pressure. The blood pressure was still 90 mm. Hg 45 to 60 minutes after the inception of fibrillation; only in that dog in which fibrillation persisted for 14 minutes did the arterial blood pressure decline markedly within a few minutes.

It seems from these experiments on the effect of procaine that the doses of procaine hydrochloride which constituted a reliable means of stopping fibrillation were such that they depressed the rhythmicity of the heart so that the ventricles remained in standstill. Smaller doses of procaine did not seem a reliable means of stopping ventricular fibrillation because too many failures were encountered or because ventricular standstill occurred with a long latent period. Therefore, procaine alone seemed to be not too promising a means of stopping fibrillation. When massage was administered after ventricular standstill had been induced by procaine or after the fibrillation had been made slower, ventricular fibrillation recurred or persisted. Massage-countershock was still effective in stopping fibrillation and restoring a normal cardiac mechanism. However, in most experiments the blood pressure did not rise, or if it did, it promptly declined to very low levels, although in a few dogs which had received 20 mg. of procaine, massage-countershock resulted in the re-establishment of normal cardiac mechanism and a fairly normal blood pressure. It is probable that massage-countershock alone would have given better results. With the hope of preventing myocardial anoxia, cardiac massage was maintained after 20 or 50 mg. of procaine had been administered to 10 dogs, but this did not improve the results observed with procaine. There was no definite indication in these experiments that procaine rendered countershock more effective in stopping ventricular fibrillation, although the possibility was not excluded by our experiments performed with hearts of relatively small size in which electrical countershock alone was eminently effective in stopping ventricular fibrillation. Our observations essentially are in agreement with those of Kay[8] as well as those of Stearns, Maison and Stutzman,[7] except for the fact that procaine alone stopped ventricular fibrillation more frequently in our series of experiments probably because heavier doses were used at least in some dogs.

It is a little more difficult to evaluate the results obtained in those experiments in which

ventricular fibrillation was allowed to persist for five minutes, after which epinephrine (0.05 or 0.01 mg. per kilogram of body weight) was injected into the ventricular cavities and 10 massages of the ventricular mass given before electrical countershock was applied. Such doses of epinephrine did not prevent the electrical countershock from stopping ventricular fibrillation. However, in three experiments numerous countershocks had to be given before ventricular fibrillation was stopped. Whether or not this was due to epinephrine cannot be determined inasmuch as such a difficulty is occasionally encountered with hearts not under the influence of epinephrine. There seems to be little doubt that such doses of epinephrine given as has been described resulted in the immediate restoration of a strong and frequent ventricular beat without massage as soon as fibrillation had been stopped by countershock. It must be kept in mind, however, that the frequent recurrence of ventricular fibrillation in this series of experiments was a definite drawback. It was not attempted to determine whether doses of epinephrine sufficiently small not to cause a recurrence of ventricular fibrillation would still be useful in restoring promptly the strength of the ventricular contraction.

Summary and Conclusions

The usefulness of electrical countershock, massage, synthetic l-epinephrine and procaine in stopping electrically-induced ventricular fibrillation and restoring a competent ventricular contraction was studied in 75 dogs anesthetized with sodium pentobarbital. The following conclusions were reached.

1. Massage alone does not stop ventricular fibrillation although it prevents it from deteriorating from the early fine, rapid type to the late slow, coarse type, or even makes it revert from the late to the early type.

2. Epinephrine alone does not stop fibrillation although it alters it to make the fibrillatory process become very fine and rapid.

3. Electrical countershock is very effective in stopping ventricular fibrillation in its early stage as well as its late stage. It also stops fibrillation when the heart is under the influence of procaine or epinephrine. When shock is applied after a relatively short period of fibrillation of approximately 30 seconds, a coordinated and competent ventricular beat promptly supervenes after fibrillation has been stopped by the countershock, and the arterial blood pressure is restored to its control level. When applied after five minutes of fibrillation, countershock stops fibrillation; a coordinated ventricular contraction is restored but it is incompetent, which, together with probable damage to other structures than the myocardium, such as the vasomotor center, prevents the restoration of an adequate circulation.

4. If the fibrillating ventricles are continuously massaged before the countershock used to stop fibrillation is applied, a coordinated competent ventricular contraction immediately follows the termination of fibrillation even when fibrillation is allowed to persist for as long as 10 minutes and possibly longer. There seems to be no advantage in trying to stop with countershock a fibrillation which has lasted more than one to two minutes before massage has been administered for an adequate period of time. The reason is that, if countershock is prematurely used, only a weak ventricular beat will follow the termination of fibrillation. If massage is then resorted to in order to prevent further deterioration of the circulation, it will again induce fibrillation in such hearts, and a series of massage-countershock-massage maneuvers will have to be administered.

5. Procaine slows the rate of the fibrillatory process or even stops fibrillation, depending upon the dose of the drug used. However, those doses of procaine, which constitute a reliable means of stopping fibrillation, depress, among other things, the rhythmicity of the heart to such an extent that after fibrillation has been stopped, long periods of ventricular standstill occur. Massage then applied induces fibrillation.

6. If after a five minute period of fibrillation, epinephrine is administered prior to the countershock, a competent ventricular contraction is resumed as soon as fibrillation has been stopped, and the blood pressure is restored to a level seen only when, under similar experimental conditions, a prolonged period of massage precedes countershock. However, with the

doses of epinephrine studied, fibrillation recurs very frequently, which necessitates the repeated use of the electrical countershock.

Sumario Español

La eficacia del contrachoque eléctrico, masaje cardíaco, epinefrina y procaina en terminar la fibrilación ventricular y restaurar contracciones ventriculares eficientes en el perro anestesiado ha sido estudiada. Se encontró que el contrachoque es una medida confiable de terminar la fibrilación. Sinembargo, debe de ser precedido de masaje cardíaco si no es aplicado prontamente luego de la iniciación de la fibrilación. La epinefrina ayuda a restaurar contracciones ventriculares eficientes una vez la fibrilación haya sido terminada con contrachoque, pero aumenta la incidencia de la reaparición de la fibrilación. Las dosis de procaina que constituyen una medida confiable para la terminación de la fibrilación deprimen el ritmo del corazón hasta tal extremo que la cesación de la fibrilación es seguida de prolongados intervalos de pausa cardíaca.

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The Syndrome of Patent Ductus Arteriosus with Pulmonary Hypertension

By Herbert Hultgren, M.D., Arthur Selzer, M.D., Ann Purdy, M.D., Emile Holman, M.D., and Frank Gerbode, M.D.

Eight cases of patent ductus arteriosus associated with marked pulmonary hypertension are presented with complete cardiac catheterization studies in six patients and autopsy studies in three cases. Four patients had clear evidence of a "reversed" shunt through the ductus, three presenting the clinical picture of cyanotic congenital heart disease. The authors discuss the nature of the increased resistance of the pulmonary vascular bed which is the basis of the circulatory changes in these cases.

THE usual uncomplicated patent ductus arteriosus presents a fairly constant clinical picture with the following diagnostic features usually present: (1) a continuous murmur in the pulmonic area; (2) an increased pulse pressure; (3) an electrocardiogram without evidence of right ventricular hypertrophy; (4) absence of cyanosis; (5) x-ray evidence of left ventricular dilatation with dilatation and active pulsation of the pulmonary arteries.

In most instances an accurate diagnosis can be made by ordinary clinical methods of study and only rarely is cardiac catheterization or angiocardiography necessary.[1] Occasionally, however, these characteristic features may be absent and accurate diagnosis may then be more difficult. This may occur in infancy and more rarely in older children and adults. The absence of a continuous murmur in infancy may be physiologic and related to the decrease in the pressure gradient between the pulmonary artery and the aorta that is present at that time.[2, 3] As the child becomes older the continuous character of the murmur usually appears and the correct diagnosis can then be made. Ziegler[2] has recently emphasized the diagnostic features of such cases.

From the Departments of Medicine, Pediatrics and Surgery of the Stanford University School of Medicine, San Francisco, Calif.

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In older children and adults an increasing number of instances of patent ductus arteriosus with an atypical clinical picture are being encountered. Most of these cases have been instances of isolated patency of the ductus arteriosus in which some or even all of the usual diagnostic features have been missing, the most common feature usually being the absence of a continuous murmur. Studies made in some of these cases have demonstrated either marked elevation of pulmonary artery pressure or postmortem evidence of its presence in the form of marked right ventricular hypertrophy.

The correct clinical recognition of this syndrome is important, for it is possible that it may be more common than the few reported cases suggest. It is important also to study these patients carefully in order to investigate the nature of the increased pulmonary vascular resistance, for this may have broad implications regarding vascular diseases of the pulmonary circulation in other conditions.

For these reasons this report of eight cases of patent ductus arteriosus with pulmonary hypertension and atypical clinical manifestations has been prepared.

Methods of Study

All cases were studied either on the wards of the Stanford Hospital (seven cases) or at the San Francisco Hospital (one case).

Cardiac catheterization studies were performed as described by Cournand.[4] Oxygen analyses were performed in a Van Slyke apparatus and single samples analyzed in different machines agreed within 0.2 volume per cent. Pressures were recorded by

means of a Hamilton manometer with a deflection of the light beam of approximately 3 cm. for every 50 mm. Hg. Mean pressures were determined by planimetric integration of the area under the pressure curve. All intracardiac pressures were measured, using the midpoint of the chest as the reference zero. In those cases in which oxygen consumption was not determined, a normal oxygen consumption was assumed, using corrections for the patient's age and body surface area. Cardiac outputs, pulmonary blood flow and the flow through the ductus were calculated, using the Fick principle. In patients with a reversed shunt the approximate volume of the right to left shunt through the ductus was approximated in the following manner: It was assumed that 60 per cent of the peripheral blood flow goes to the lower portion of the body. That this is approximately correct is suggested by these facts: (1) The cross section area of the descending portion of the thoracic aorta immediately below the left subclavian artery is 55 per cent of the cross section area of the aorta just above the aortic valves, using 2.0 cm. as the diameter of the descending aorta and 2.7 as the diameter of the aorta above the valves.[5] (2) Blalock's[6] study of blood flow in the superior and inferior venae cavae gave a ratio of 60 per cent of the venous return flowing through the inferior cava and 40 per cent flowing through the superior vena cava, which is roughly comparable to these figures. (3) Studies of inferior vena caval and superior vena caval flows done in this laboratory, using the Fick principle, gave similar ratios.[7] The left ventricular output was assumed to be equal to the total pulmonary blood flow. If 60 per cent of the left ventricular output enters the descending aorta and mixes with blood of a lower oxygen saturation coming through the ductus, the volume of this shunt through the ductus can be crudely calculated by the following general mixing formula:

$$O_2\ content_{AA} = \frac{Flow_{DA}\,(O_2\ content_{DA}) + flow_{PD}\,(O_2\ content_{PD})}{flow_{DA} + flow_{PD}}$$

The following abbreviations are used: *AA* equals abdominal aorta or that portion of the aorta distal to the orifice of the ductus. *DA* equals descending aorta or that portion of the thoracic aorta proximal to the orifice of the ductus but distal to the origin of the left subclavian artery. *PD* equals patent ductus. The vascular resistance of the pulmonary circulation was calculated according to the formula:

$$R = \frac{PA_m \times 1.332 \times 60}{PF}$$

R equals vascular resistance in dynes per centimeter[5] per second; PA_m equals mean pressure in the pulmonary artery in mm. Hg; *PF* equals pulmonary blood flow in liters per minute. Predicted resistances were obtained using normal mean pressures and blood flows[8] and corrected for body surface area.

Kerosene perfusion of the lungs obtained at autopsy was performed in one case. The technic is similar to that used in previous studies of the coronary and renal vascular bed.[9, 10] After rigor has disappeared the lungs are inflated in an air-tight chamber by a negative chamber pressure of 7 mm. Hg and repeated perfusions are performed at various pressures until duplicate measurements agree to within 5 per cent. After perfusion a lead carbonate and gelatin injection mass is forced into the pulmonary artery and roentgenograms are made.

Case Reports

Four cases exhibited varying degrees of cyanosis and polycythemia with evidence of a reversal of flow through the ductus.

Case 1, J. J. This 16 year old schoolgirl entered the Stanford Hospital on June 19, 1948. At the age of 9 months, a heart murmur was noted. Easy fatigue and exertional dyspnea had been noted since childhood. Five months prior to entry dyspnea had become more severe, and one month prior to entry the patient developed intractable vomiting which subsided only after being placed in an oxygen tent. During the preceding 10 years she had experienced frequent attacks of "pneumonia" with cough, increased dyspnea and fever.

Physical examination revealed a moderately dyspneic young girl with distinct cyanosis of the lips and nail beds. The blood pressure was 110/96. At the third intercostal space along the left sternal border a loud diastolic murmur and a diastolic thrill were noted. The second pulmonic sound was loud and a presystolic gallop was heard at the apex. A tender liver edge was felt 2 cm. below the costal margin. There was distinct clubbing of the fingers.

The erythrocytes were 6.1 million with 18.7 Gm. of hemoglobin and the packed cell volume was 65 per cent. The blood urea was 80 mg. per 100 ml. and the arm-to-tongue circulation time (Decholin) was 34 seconds. The venous pressure was 18 cm. of saline above the midchest. The electrocardiogram (fig. 1) revealed a right axis deviation, tall P waves in leads II and III and a deep S wave in lead CR_4. A phonocardiogram (fig. 2) revealed a split first sound, a presystolic gallop and a prominent diastolic murmur along the left sternal border. X-ray films of the heart and lungs (fig. 3) revealed enlargement of the right ventricle and a marked prominence of the pulmonary artery and its branches. Digitalis was given without producing improvement and the patient became more dyspneic, finally comatose and died on the thirteenth hospital day.

The pertinent autopsy findings were confined to the heart and lungs. The heart was grossly enlarged and weighed 400 Gm. The right ventricle was

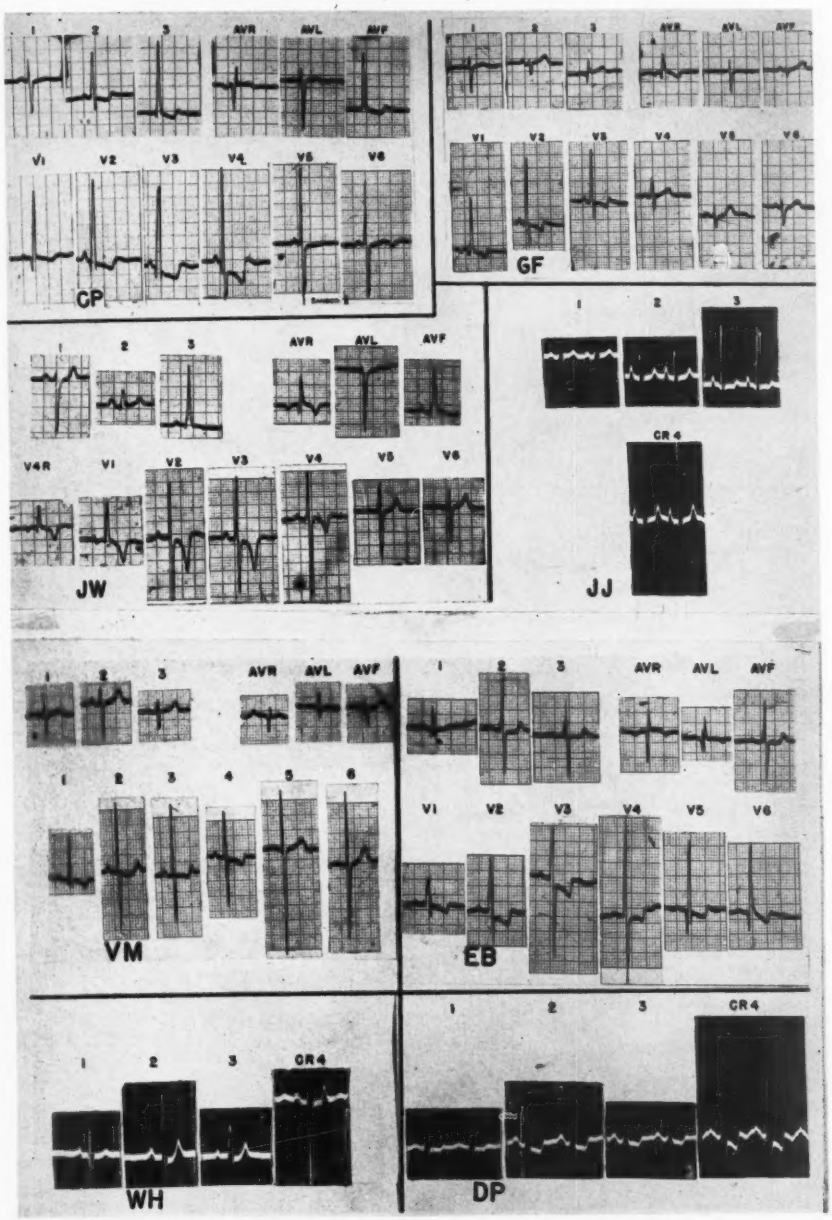

FIG. 1. Electrocardiograms from all patients. The upper four tracings from patients demonstrating right to left shunts show pattern of right ventricular hypertrophy.

hypertrophied and dilated and its myocardium measured 5 mm. in thickness compared with that of the left ventricle which measured 9 mm. in thickness. When both ventricles were dissected away from the septum the right ventricle weighed 167 Gm. and the left 78 Gm. The pulmonary artery was dilated and its wall was as thick as the wall of the aorta. A patent ductus arteriosus measuring 8

mm. in diameter and 4 mm. in length connected the aorta and pulmonary artery (fig. 4). The foramen ovale was closed and the interventricular septum was intact. The smaller branches of the pulmonary artery were thickened and stood out prominently from the cut surface of the lung. The lungs weighed 450 Gm. together and they appeared normal.

media was composed largely of collagenous tissue. The other organs were not remarkable.

Both lungs perfused with kerosene. A marked decrease in perfusibility was observed, amounting to less than one tenth that of the perfusibility of normal lungs. During perfusion of the pulmonary artery backflow of kerosene through the bronchial arteries was noted. These arteries were 1 to 2 mm.

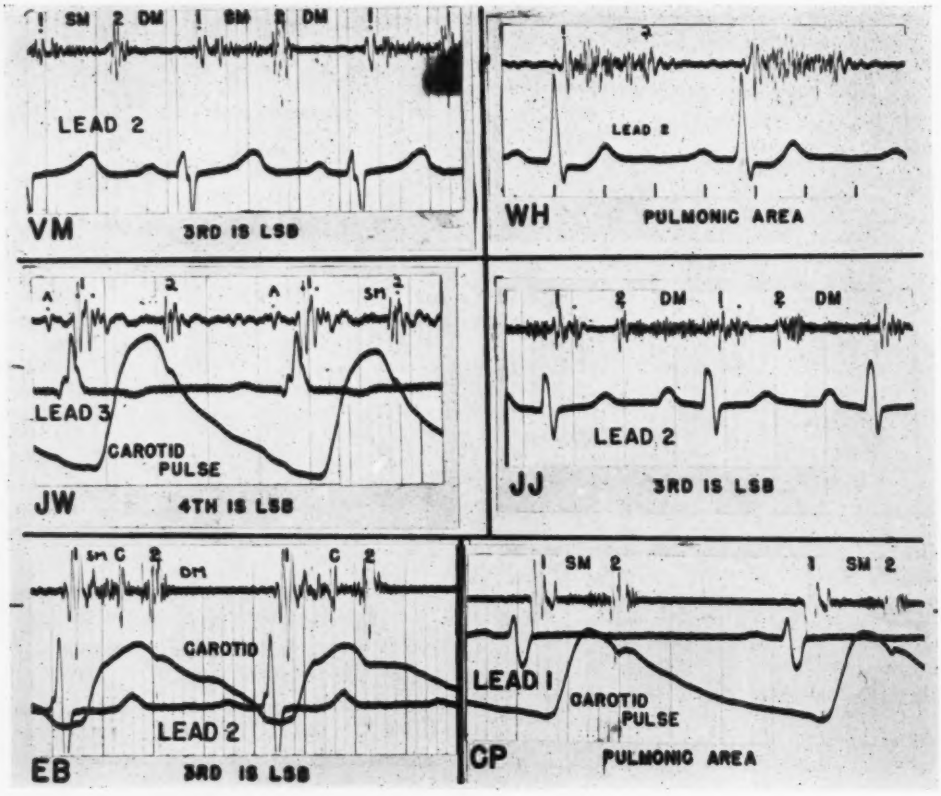

FIG. 2. Phonocardiograms with simultaneous electrocardiograms on six patients showing murmurs.

Microscopically many of the smaller branches of the pulmonary artery were occluded by thrombi, some of which were recent and showed beginning organization as manifested by invasion of fibroblasts. Other thrombi were recanalized so that two or more distinct endothelial lined lumina were present, some of which contained red cells (fig. 5). Many small arteries and arterioles had a conspicuous thickening of the media and the elastica interna. There was no evidence of arteritis and the lung tissue appeared normal. The aorta adjacent to the ductus was normal. The intima of the ductus was thickened and a definite elastica interna was present. The

in outside diameter at their origins. After perfusion the pulmonary arterial tree of one lung was injected, roentgenograms were made and compared with a normal lung similarly treated (fig. 4). In contrast to the fine, branching vascular pattern of the normal lung the patient's lung revealed an obliteration of the finer terminal branches, the injection mass ending abruptly in vessels approximately 1 mm. in diameter. A few fine long vessels were seen which paralleled the main branches and which may have been bronchial collateral vessels filled by retrograde injection.

Case 2, G. F. This 34 year old white American housewife entered Stanford Hospital on May 15, 1950. Cyanosis had been noted by the parents at the age of two. Her activity had been moderately restricted in school because of exertional dyspnea and weakness. Fluoroscopic examination at 24 because of a cough revealed cardiac enlargement. Her exercise tolerance had been good and she had been able to do all her own housework and outdoor work on a ranch as well.

Physical examination revealed a well developed woman with a diffuse dusky cyanosis of the mucous membranes. The blood pressure in the right arm was 100/70. A slight bulge of the rib cage was present over the precordium to the left of the sternum. The second pulmonic sound was moderately loud and split. No murmurs were heard. The femoral pulses were easily felt. There was no clubbing of the fingers but distinct clubbing of the toes was present.

The erythrocytes were 8.0 million with 24 Gm. of hemoglobin and the packed cell volume was 65 per cent The vital capacity was 3.7 liters and the venous pressure was 8.5 cm. of saline above the midpoint of the chest. The arm-to-lung circulation time (ether) was 11.5 seconds and the arm-to-tongue circulation time (Decholin) was 21 seconds. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films of the chest (fig. 3) revealed enlargement of the right ventricle with prominence of the pulmonary conus. The lung fields were clear. An angiocardiogram using 30 cc. of 75 per cent Neoiopax

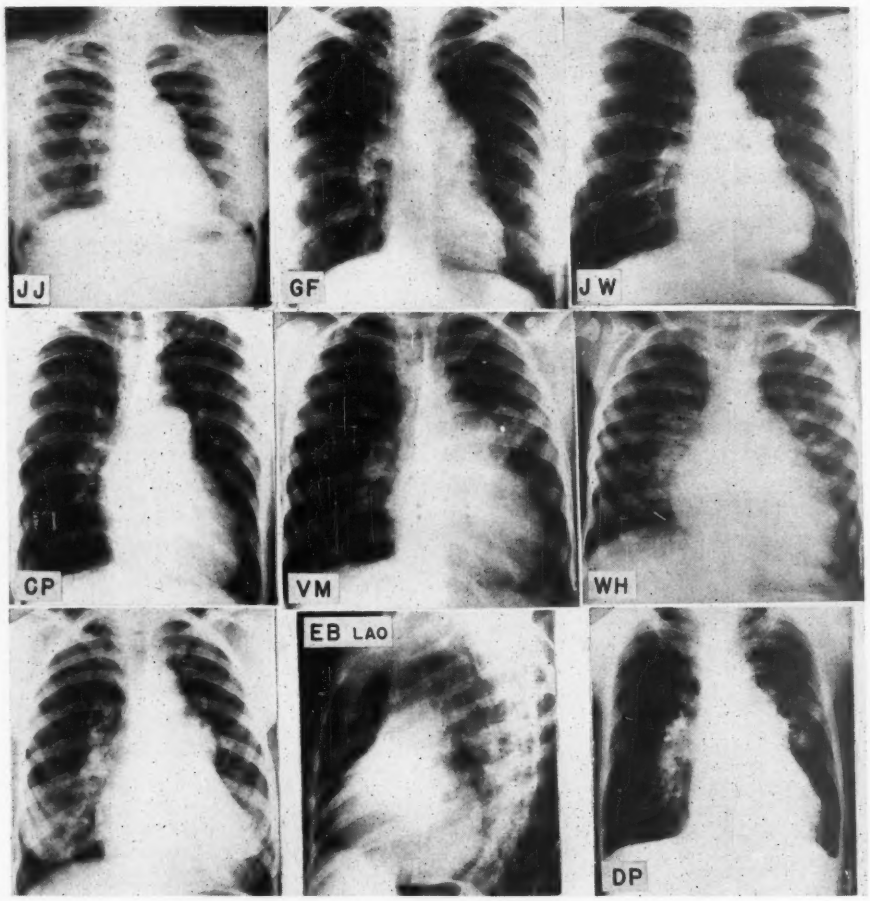

FIG. 3. Anteroposterior roentgenograms of chests showing enlargement of pulmonary arteries. Left anterior oblique view of patient E. B. indicates moderate degree of left ventricular enlargement.

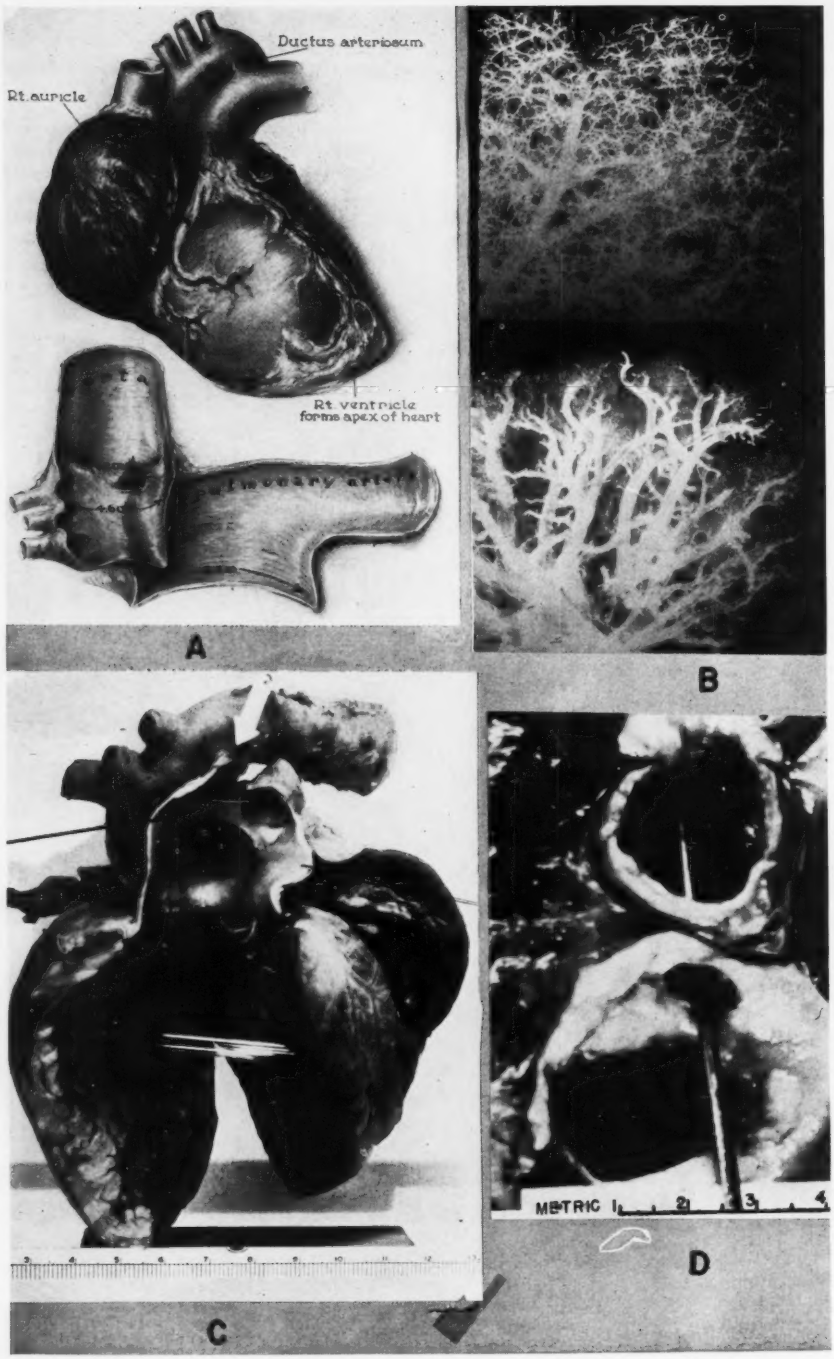

FIG. 4. *A*. Patient J. J. Artist's drawing of gross specimen.

B. X-ray photograph of portion of normal lung above and a similar portion of lung from patient J. J. below. The pulmonary artery has been injected with a radio-opaque medium.

C. Patient V. M. Autopsy specimen of heart showing location of ductus. Note marked hypertrophy of right ventricle.

D. Patient D. P. Looking down at the cut ends of the pulmonary artery (below) and the aorta (above) showing probe in the ductus. Note dilatation and atherosclerosis of pulmonary artery.

evealed prompt opacification of the right ventricle, ulmonary artery and descending aorta. Some of he contrast media was also seen in the arch of the orta as well. The results of the cardiac catheterization studies are indicated in table 1*A*.

In May 1951, the patient re-entered the hospital or additional studies. There had been no change in ymptoms, physical examination or x-ray examination. The erythrocytes were 7.2 million, the hemoglobin 22.3 Gm. and the packed cell volume was 5 per cent. Under local anesthesia Cournand needles were inserted into the left femoral and left brachial arteries and blood samples were withdrawn at rest and immediately after exercise with the results indicated in table 1*B*.

Comment. The evidence of arterial unsaturation in the lower extremities, clubbing of the toes but not of the fingers and marked polycythemia clearly establishes the diagnosis of a patent ductus arteriosus with pulmonary hypertension and a right to left shunt. The striking clinical feature was the absence of any detectable heart murmur although the pulmonic second sound was clearly accentuated.

Case 3, J. W. This 31 year old white Canadian bus driver entered the Stanford Hospital on April 23, 1951. During childhood his parents had noted that he became dyspneic easily. A faint heart murmur was first noted at 20 years in a routine examination. His exercise capacity had been only slightly impaired and he had worked as a laborer for many years. During the past six months he had noted more dyspnea, occasional attacks of precordial pain and cyanosis of the lips occurring on exertion.

Physical examination revealed a muscular man with moderate erythema of the lips. The blood pressure in the right arm was 120/80. A diffuse precordial heave was palpable and the second pulmonic sound was loud and split. At the fourth intercostal space along the left sternal border there was a grade II, well localized systolic murmur. A nontender liver edge was felt at the costal margin. There was slight but distinct clubbing and erythema of the tips of fingers and toes.

The hemoglobin was 21 Gm. and the packed cell volume 64 per cent. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films (fig. 3) revealed right ventricular enlargement with prominence of the pulmonary artery. There was no evidence of left ventricular enlargement. A phonocardiogram (fig. 2) revealed a split first sound (1), an auricular sound (a) and a grade II systolic murmur (SM). On April 23, 1951, cardiac catheterization studies were performed and the results are summarized in table 2. Four hours after the procedure a sample of femoral artery blood was removed for oxygen analyses.

Comment. It is of interest that distinct clubbing of both fingers and toes was present despite the distinct difference in oxygen saturations between brachial and femoral arteries. The very low oxygen content of femoral artery blood suggests a very large right to left shunt.

Case 4, C. P. This 21 year old white American student entered the hospital on Feb. 19, 1952. At the age of 5 years a heart murmur was detected during a routine examination. Since that time cyanosis of the lips and extremities had been noted during exertion and in cold weather. Exercise capacity had always been moderately limited and severe exertion produced weakness of the legs and dyspnea. There was no history of hemoptyses, squatting or symptoms of heart failure.

Physical examination revealed a thin boy with distinct erythema of the cheeks, lips and tips of fingers and toes. The neck veins were not distended. The blood pressure in the right arm was 110/80 mm. Hg. There was a slight bulge of the precordium along the left sternal border. The second pulmonic sound was loud and accompanied by a faintly palpable shock. In the fifth intercostal space along the left sternal border a grade III blowing murmur filled systole. At the pulmonic area a somewhat fainter systolic murmur was present which became loudest just before the second sound. The femoral and pedal pulses were easily felt. There was no clubbing of the digits.

The hemoglobin was 22.7 Gm. and the packed cell volume varied from 67 to 69 per cent. The electrocardiogram (fig. 1) revealed changes compatible with right ventricular hypertrophy. X-ray films (fig. 3) revealed right ventricular enlargement and moderate prominence of the pulmonary arteries which did not show diminished pulsations. A phonocardiogram (fig. 2) confirmed the presence of the murmurs noted clinically. On March 14, 1952, cardiac catheterization studies were performed with the results indicated in table 3. Angiocardiography was performed, using 35 cc. of Neoiopax. Slow filling of the right ventricle and pulmonary vessels occurred and the aorta and ductus arteriosus were not visualized.

Comment. The difference in oxygen content between the brachial and femoral arteries clearly indicates the presence of a reversed shunt through the ductus.

Four cases exhibited no evidence of a right to left shunt through the ductus but had an atypical clinical picture with marked pulmonary hypertension.

Case 5, V. M. This 7 year old white American child from the San Joaquin Valley entered the hospital on Jan. 9, 1950. At the age of 2 months a persistent cough appeared and a heart murmur was heard. X-ray films revealed cardiac enlargement. Since infancy the child became tired easily and

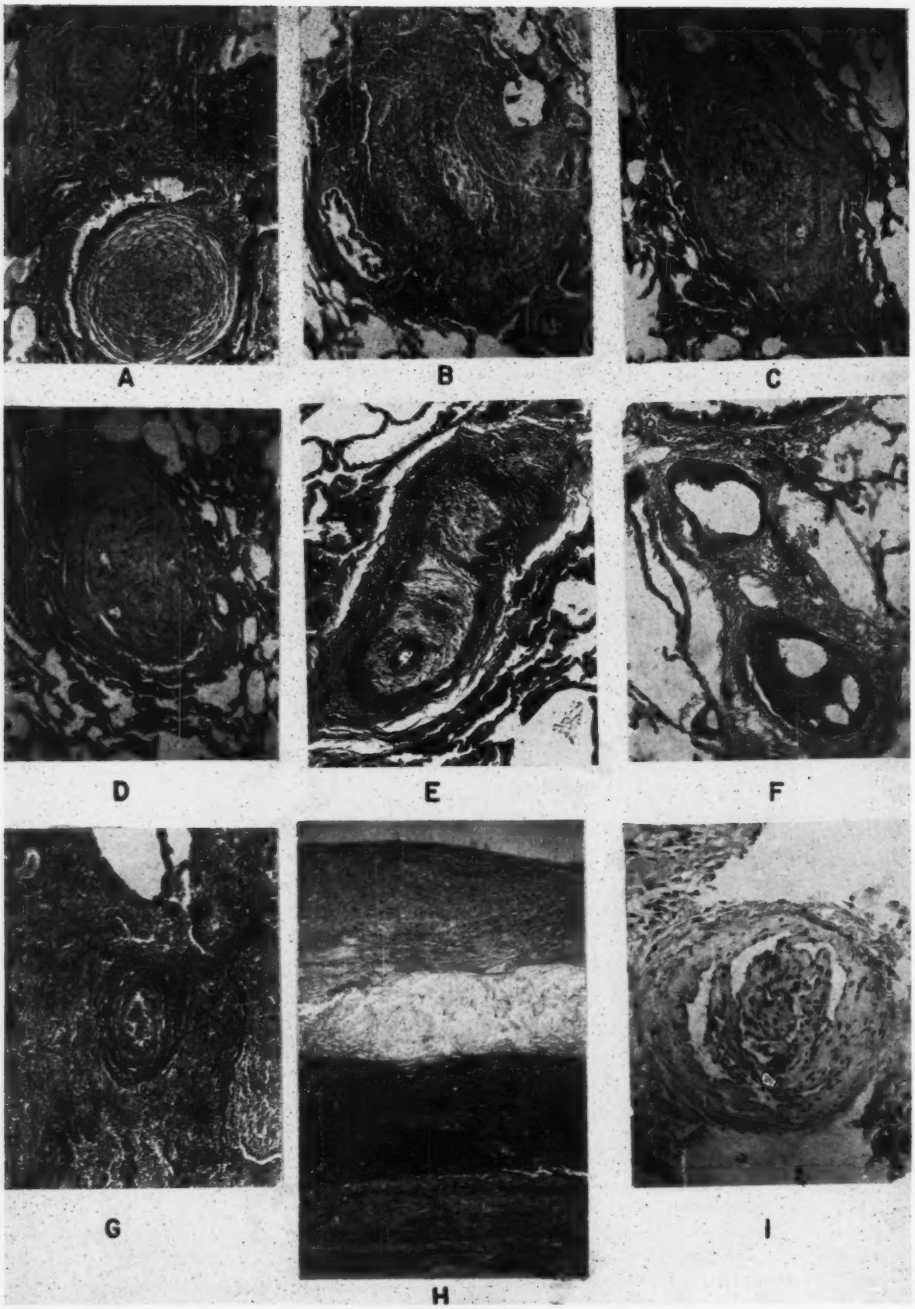

FIG. 5 *A*. Patient V. M. Small pulmonary artery at upper left with marked luminal narrowing due to intimal proliferation and medial hypertrophy. Tubercle of coccidioidomycosis below with adjacent lymphocytic infiltration. Hematoxylin and eosin × 112.

B. Patient V. M. Acute pulmonary arteritis with destruction and infiltration of arterial wall by polymorphonuclear leukocytes. H. and E. × 48.

C. Patient V. M. Occlusion of small pulmonary artery by fibrous tissue containing scattered polymorphonuclear leukocytes. Surrounding inflammatory process still present. H. and E. × 48.

D. Patient V. M. Occlusion of small pulmonary artery by fibrous tissue with recanalization by small endothelial lined lumina containing erythrocytes. H. and E. × 48.

E. Patient V. M. Recanalization of fibrous occlusion of small pulmonary artery. Van Gieson × 112.

dyspnea was evident on mild exertion. Bilateral congenital cataracts were repaired surgically at 2 years. Seven months before entry a fever of 104 F. developed and lasted for 12 days. X-ray films revealed a small area of density in the posterior portion of the left upper lobe.

TABLE 1.—*Findings on Catheterization in Case 2*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
A		
Inf. v.c.	17.0	
Sup. v.c.	20.1	
Av. both v.c.	18.6	
Upper rt. at.	19.3	
Mid. rt. at.	18.8	0
Low rt. at.	19.2	
Low rt. vent.	19.4	
Lat. rt. vent.	19.2	102/4
High rt. vent.	19.3	
P.A.	20.1	
P.A.	20.9	104/64/72
P.A.	20.5	
Rt. br. art.		
Rest	26.3 (93)	88/56/74
Exercise	25.7 (91)	
O_2 cap.	28.3	
B		
Lt. br. art.		
Rest	26.8 (91)	
Exercise	25.7 (87)	
Left fem. art.		
Rest	24.7 (84)	
Exercise	20.9 (71)	
O_2 cap.	29.6	

Abbreviations: V.C. = vena cava. At. = atrium. Vent. = ventricle. P.A. = pulmonary artery. Br. = brachial. Fem. = femoral.

Physical examination revealed a thin, pale, stoop-shouldered little girl with bilateral, repaired cataracts. There was moderate kyphosis of the dorsal spine and a prominent bulge of the rib cage over the left precordium. The blood pressure in the right arm was 100/60. There was a prominent precordial heave. The second pulmonic sound was very loud and it was followed by a harsh diastolic murmur heard along the left sternal border. A loud systolic murmur was present over the pulmonic area. There was a moderate systolic pulsation of the neck vessels but no venous distention. There was no clubbing of the digits.

TABLE 2.—*Findings on Catheterization in Case 3*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
Inf. v.c.	18.9	
Sup. v.c.	19.6	
Av. both v.c.	19.3	
Rt. at. (rest)	18.4	8/0
Low rt. vent.	18.0	
High rt. vent.	17.8	134/12
P.A.		
Rest	19.1	130/82/106
Exercise	11.5	168/106/137
Rt. br. art. (rest)	24.2 (86)	
Left br. art.		
Rest	25.5 (91)	128/76/9
Exercise	24.9 (89)	171/96
Fem. art.* (rest)	17.2 (61)	
O_2 cap.	28.1	

* Sample obtained four hours after cardiac catheterization.

Abbreviations as in table 1.

TABLE 3.—*Findings on Catheterization in Case 4*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
Inf. v.c.	18.9	
Sup. v.c.	20.1	
Av. both v.c.	19.5	
Rt. at.	19.5	
Low rt. vent.	19.4	
High rt. vent.	20.2	134/10
Main P.A.	20.4	127/64/100
Main P.A.	21.1	
Rt. P.A.	20.3	
Br. art. (rest)	27.8 (95)	110/80
Fem. art. (rest)	24.0 (82)	110/66/84
O_2 cap.	29.2	

The hemoglobin was 14.0 Gm. and the packed cell volume was 40 per cent. The electrocardiogram (fig. 1) revealed changes which were compatible

F. Patient J. J. Small pulmonary arteries containing recanalized organized thrombi.

G. Patient D. P. Small pulmonary artery showing fibrous intimal thickening with moderate luminal narrowing. The surrounding lung tissue shows dense erythrocytic infiltration of the alveoli. H. and E. × 112.

H. Patient D. P. Section through wall of main pulmonary artery. Note marked thickening of intima (top) with typical atheroma formation. A tiny fibrous scar is present in the outer portion of the media. The adventitia (bottom) is normal. Van Gieson × 48.

I. Patient E. B. Pulmonary arteriole showing obliteration of lumen by cellular fibrous tissue and recanalization by prominent endothelial lined spaces containing erythrocytes.

with right ventricular hypertrophy. X-ray films (fig. 3) revealed cardiac enlargement involving largely the right ventricle and prominence of the pulmonary arteries with moderate pulmonary congestion. Exaggerated pulsations of the pulmonary arteries were noted during fluoroscopy. A 3 cm. irregular density was present in the second left intercostal space. Phonocardiograms (fig. 2) confirmed the presence of the murmurs noted clinically. An angiocardiogram, using 75 per cent Diodrast, revealed an enlarged right ventricle, dilated pulmonary arteries and possibly late recirculation of the contrast material through the pulmonary vessels. Cardiac catheterization studies were performed on Jan. 11, 1950, using Avertin and local anesthesia. The results are summarized in table 4.

On July 29, 1950, the child was admitted to the Childrens Hospital of San Francisco. Three weeks

TABLE 4.—*Findings on Catheterization in Case 5*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
Inf. v.c.	11.8	
Sup. v.c.	8.8	
Av. both v.c.	10.3	
Upper rt. at.	11.3	
Mid. rt. at.	10.4	/ /5
Low rt. at.	10.0	
Low rt. vent.	10.9	
Mid. rt. vent.	10.8	80/8
Upper rt. vent.	10.9	
Rt. P.A.	12.1	
Main P.A.	12.3	80/40/62
Fem. art. start	14.6 (93)	114/56/83
Fem. art. end	14.0 (89)	134/62/95
O_2 cap.	15.8	

prior to entry she had developed a nonproductive cough, and fever and edema of the feet had been noted. Physical examination revealed a heart rate of 128 per minute, a blood pressure of 110/80 and a rectal temperature of 37.4. There was distention of the neck veins, moist rales throughout both lung fields, enlargement of the liver and moderate peripheral and sacral edema. Despite the prompt administration of digitoxin and oxygen, the child died 12 hours after entry.

The principal findings of the autopsy examination were related to the heart and lungs. The heart was greatly enlarged due to dilatation and hypertrophy of both ventricles (fig. 4). The right ventricular myocardium measured 7 mm. in thickness and the left ventricular myocardium 12 mm. The pulmonary valve leaflets were fused at the commissures and the free edges were smooth but thickened and retracted so as to produce an insufficiency without stenosis. The pulmonary artery was enlarged and its wall was as thick as that of the aorta. The pulmonary artery measured 5.7 cm. in circumference just above the valve and the aorta 4 cm. in circumference at a comparable level. All of the branches of the pulmonary artery were thick walled and dilated and their cut ends protruded rigidly from the cut surface of the lungs. No emboli or thrombi were noted in any of the branches. At a point 1 cm. beyond the bifurcation of the left pulmonary artery the opening of a short but widely patent ductus arteriosus was present; the ductus measured 3 mm. long and 4.5 mm. in diameter after formalin fixation. No vegetations were present in or near either end of the ductus. The foramen ovale was functionally closed but admitted a 1 mm. probe. The ventricular septum was intact. No intracardiac thrombi were noted.

One hundred and fifty cubic centimeters of clear fluid were present in the right pleural cavity. In the upper lobe of the left lung a pale, firm 4 by 6 cm. area of gray-white tissue was present. It was adherent to the parietal pericardium at one point and in the center of the area was a single, hard, white 15 mm. nodule which contained no calcium. Numerous small 1 to 2 mm. pale nodules were scattered around the periphery of the large mass of tissue. No nodules were present in the left lower lobe or in the right lung. The mediastinal lymph nodes on the left were moderately enlarged but did not appear abnormal externally or after incision. The abdominal organs were moderately congested but otherwise normal.

Sections of the left lung revealed numerous small tubercles, some of which had fused into granulomatous masses in which numerous, multinucleated giant cells of the Langhans variety were present (fig. 5). In occasional giant cells small double contoured spherules characteristic of coccidiomycosis were present. No tubercles were present in the right lung. The smaller branches of the pulmonary artery, throughout both lungs, measuring from 0.1 mm. to 2 mm. in diameter, revealed a diffuse arteritis consisting in occasional areas of an infiltration of all layers of the vessel wall with polymorphonuclear leukocytes, obliteration of the lumen by thrombosis and destruction of the wall. Eosinophils were scarce. Other areas revealed an apparently healed arteritis without evidence of acute inflammation but with fibrous scarring of a disrupted vessel wall and secondary recanalization of a well organized luminal thrombus. The arteritis was not related to the granuloma since it involved the vessels of both lungs and no tubercles or giant cells were present in the arterial lesions. Smaller arterioles revealed concentric intimal thickening with luminal narrowing or obliteration and occasional prominent medial deposits of hyaline material. The pulmonary valve was composed of dense acellular fibrous tissue in which no lymphocytes or blood vessels were seen.

Comment. The very prominent diastolic murmur

was probably related to the deformity of the pulmonic valve as well as to the high pressure in the pulmonary artery. The etiology of the valve deformity is unknown. No other valves were deformed and no scars were found in the heart, hence it was probably not of rheumatic origin. A congenital deformity seems most likely.

Case 6, W. H. This 4 year old white American child entered the hospital on May 25, 1949. Cyanosis was noted during the first weeks of life when oxygen was required frequently and "blue spells" with convulsions occurred during feedings. A heart murmur and thrill were noted at the age of 1 week. Development, however, was subsequently normal. Exercise capacity was moderately limited.

Physical examination revealed a thin boy with a blood pressure of 95/35. There was no venous distention but marked pulsations of the carotid vessels were noted and a distinct thrill was felt during systole in the suprasternal notch. There was a moderate anterior bulge of the chest wall over the left precordium. The heart was enlarged to the right and left. The second pulmonic sound was loud. A rough, grade IV systolic murmur was present over the entire precordium and heard along the carotid and brachial arteries as well. The murmur was accompanied by a prominent thrill. At the apex a short, faint mid-diastolic murmur was present. There was no clubbing of the digits and the femoral arteries were easily felt.

The hemoglobin was 11.7 Gm. and the packed cell volume 34 per cent. The arm-to-lip circulation time (fluorescein) was 10 seconds. The electrocardiogram was thought to be compatible with cardiac hypertrophy, probably involving both ventricles. X-ray films (fig. 3) revealed enlargement of both right and left ventricles with a prominence of the pulmonary arteries and moderate pulmonary congestion. Oblique views revealed moderate enlargement of the left auricle. Phonocardiograms (fig. 2) revealed a loud murmur filling systole and no evidence of a diastolic murmur. Angiocardiograms, using 20 cc. of 75 per cent Diodrast, revealed no evidence of an overriding aorta, apparent recirculation of the contrast media in the pulmonary artery after its appearance in the aorta and the presence of a small "ductus diverticulum" directed anteriorly from the first part of the descending aorta. On May 31, 1949, cardiac catheterization studies were performed under Pentothal anesthesia. A number 6 cardiac catheter was guided without difficulty into the right ventricle, pulmonary artery and through a patent ductus into the descending aorta. The essential findings are summarized in table 5. On March 27, 1951, cardiac catheterization was repeated by Dr. Sidney Sobin with essentially similar results, the catheter again passing from the pulmonary artery through the ductus and into the aorta.

Subsequently at operation a large patent ductus was ligated and divided. A follow-up report obtained through the courtesy of Dr. Louis Martin indicated that there has been marked clinical improvement but that a somewhat less intense systolic murmur is still present at the fourth intercostal space along the left sternal border.

Comment. This patient possibly also had an interventricular septal defect as evidenced by: (a) catheterization studies indicating a rise of 0.8 volume per cent in oxygen from right auricle (average oxygen 8.8) to right ventricle; (b) the persistence of the loud precordial systolic murmur and thrill after ligation and division of the ductus.

Case 7, E. B. This 33 year old white American housewife entered the hospital on March 25, 1952. Her mother had developed rubella during the third or fourth month of pregnancy. A heart murmur was first noted at the age of two years. Growth was slow and the patient had always been slender and under normal weight. She had developed frequent bouts of pneumonia as a child and also had pneumonia and a prolonged convalescence following a cesarean section at the age of 27. In the past two years she had noted slight exertional dyspnea.

TABLE 5.—*Findings on Catheterization in Case 6*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
Inf. v.c.	9.0	
Sup. v.c.	8.7	
Rt. at.	8.2	/ /9
Rt. at.	9.9	
Rt. at.	8.4	
Rt. vent.	10.6	95/15
P.A.	11.1	93/65/86
Desc. aorta	13.5	102/53
Fem. art. (rest)	13.7 (89)	100/30/63
O_2 cap.	15.3	

Desc. = descending.

Physical examination revealed a thin woman with a blood pressure on several occasions varying from 135/65 to 150/80. There was an accentuation of visible carotid pulsations in the neck. A distinct bulge of the rib cage over the left precordium was noted. There was a prominent heave to the left of the sternum, and at the second intercostal space along the left sternal border a systolic thrill and a palpable pulmonic shock was present. A loud grade IV systolic murmur was present along the left sternal border and in midsystole a prominent click was noted which was louder during expiration. The second pulmonic sound was accentuated and followed by a high pitched, faint, blowing diastolic murmur heard only just beneath the pulmonic area.

The hemoglobin was 13 Gm. and the packed cell volume was 40 per cent. The electrocardiogram (fig. 1) showed changes compatible with both left and right ventricular hypertrophy. A phonocardiogram (fig. 2) confirmed the presence of the murmurs and sounds noted clinically. X-ray studies, including fluoroscopy, revealed enlargement of both right and left ventricles, a normal sized aorta and prominence of the pulmonary arteries which pulsated vigorously (fig. 3). On March 27, 1952, cardiac catheterization studies were performed with the results indicated in table 6.

TABLE 6.—*Findings on Catheterization in Case 7*

Location	O_2 Content cc./100 cc. and % Saturation	Pressure mm. Hg s/d/mean
Patient E. B. Preoperative studies		
Inf. v.c.	9.1	
Sup. v.c.	11.3	
Av. both v.c.	10.2	
Rt. at.	9.8	
Low rt. vent.	9.9	
High rt. vent.	10.9	100/10
Right P.A.	12.9	
Main P.A.	14.2	100/62/78
Br. art. (rest)	17.1 (96)	
Fem. art. (rest)	15.5 (87)	136/55/91
Fem. art. (exer.)	15.4 (87)	
O_2 cap.	17.7	
Patient E. B. Postoperative studies		
Inf. v.c.	9.8	
Sup. v.c.	8.4	
Av. both v.c.	9.1	
Rt. at.	9.7	
Rt. vent. (rest)	8.5	65/4
Rt. vent. (exer.)	7.4	69/4
P.A. (rest)	8.4	65/40/53
P.A. (exer.)		71/46/57
Fem. art. (rest)	13.0 (93)	130/92
Fem. art. (exer.)	13.2 (94)	130/92
O_2 cap.	14.0	

On May 15, 1952, surgery was performed and a large patent ductus 1.5 cm. long and 1.6 cm. in outside diameter was found connecting the aorta and the left pulmonary artery near the origin from he main pulmonary artery.

The following mean pressure measurements were recorded:

1. Ductus open
   - Aorta 73 mm. Hg
   - Pulmonary artery 65 mm. Hg
2. Ductus closed
   - Aorta 83 mm. Hg
   - Pulmonary artery 55 mm. Hg

The ductus was clamped, divided and the ends were sutured with silk. The patient's convalescence was uneventful and she left the hospital on the tenth postoperative day. At that time her blood pressure was 160/80 and a rough grade III systolic murmur was present at the third intercostal space along the left sternal border with accentuation of the pulmonic second sound. No diastolic murmur was heard. A lung biopsy was made during surgery. Histologic examination revealed one small artery, the lumen of which was nearly filled with a mass of connective tissue in which there were several irregular endothelial-lined spaces containing a few red blood cells. The appearance suggested thrombosis with recanalization (fig. 5).

On June 24, 1952, the patient was again studied in the hospital. She had noted no dyspnea or orthopnea since her operation and was doing all her housework and shopping without symptoms. Physical examination revealed only a faint grade I systolic murmur over the pulmonic area and only moderate accentuation of the pulmonic second sound. The systolic click noted prior to surgery was no longer audible. The blood pressure was 120/80. The electrocardiogram was unchanged but x-ray films revealed a distinct decrease in heart size and in the degree of pulmonary congestion. Cardiac catheterization studies were performed with the results summarized in table 6.

Comment. The catheterization studies indicated the presence of a fairly large left to right shunt through a patent ductus, pulmonary hypertension and probably a small right to left shunt through the ductus in part of the cardiac cycle as evidenced by a lower oxygen saturation in the femoral artery than in the brachial artery. Exercise did not increase the magnitude of this "reversed shunt." Because of this fact and also because of the large magnitude of the left to right shunt, operation was advised in the hope that a decrease in the total pulmonary flow would result in a lowering of the pulmonary artery pressure. That this occurred is indicated in the table. However the pulmonary vascular resistance is still elevated above normal, probably due to vascular occlusions of the type encountered in the lung biopsy. Whether these will regress in the course of time remains to be seen. The rise in femoral artery diastolic pressure following surgery is striking and emphasizes the importance of a low diastolic pressure as an indication of a patent ductus with a left to right shunt.

Case 8, D. P. This 48 year old white American cook and laborer entered the San Francisco Hospital for the first time on Dec. 22, 1941. At the age of 7, a heart murmur was heard. In subsequent years he was told he had an enlarged heart and a "leaky valve." In December 1941, following a period of overwork, he developed severe dyspnea, orthopnea, palpitation, weakness and a sharp, non-radiating precordial pain of 24 hours duration and entered the hospital.

Physical examination revealed a dyspneic, orthopneic man whose blood pressure varied from 142/64 to 136/70. The neck veins were distended and there was a distinct bulge of the rib cage over the left precordium. There was a visibly exaggerated pulsation of the carotid arteries. The chest was of an emphysematous contour and many moist rales were present at the bases. A diffuse precordial heave was easily felt and a loud systolic murmur was heard over the entire precordium, being loudest at the apex. Following a loud second pulmonic sound, a faint blowing diastolic murmur was heard along the left sternal border.

The erythrocytes were 4.9 million and the hemoglobin 15.8 Gm. The packed cell volume was 43 per cent. The Wassermann and Mazzini tests for syphilis were negative. An electrocardiogram (fig. 1) revealed diphasic T waves and depressed S-T segments in the limb leads, a prominent S wave in lead I and a diphasic T wave with a depressed S-T segment in CR_4. X-ray films (fig. 3) and fluoroscopy revealed a prominent "hilar dance," moderate enlargement of the right ventricle and pulmonary arteries and prominent pulmonary vascular shadows. The patient improved and was discharged a month after entry.

Eighteen months after leaving the hospital he noted the presence of tarry and bloody stools for two weeks and entered obviously anemic and in congestive failure again. The erythrocytes were 2.0 million and the hemoglobin was 6.9 Gm. Auricular fibrillation was present. A gastrointestinal x-ray study including a barium enema was not remarkable. Despite careful therapy his congestive failure became more severe and he expired five months after entry.

Autopsy revealed a large heart weighing 660 Gm. and marked hypertrophy of the right ventricle. When dissected free of the septum the right ventricle weighed 250 Gm. and the left ventricle 200 Gm. The right ventricular myocardium was 14 mm. thick and the left ventricular myocardium was 12 mm. thick. The leaflets of the aortic valve were thickened and fused at their margins up to 1 cm. from the base of the leaflets. A moderate amount of calcium was present in the thickened valves but there was no appreciable narrowing of the valve orifice. The pulmonary artery was dilated and its wall was equal in thickness to the wall of the aorta. Both the pulmonary artery and the aorta contained numerous longitudinal intimal striae and wrinkles strongly suggestive of syphilis and there were frequent calcified plaques measuring up to 2 cm. in diameter. The dilatation and thickening of the pulmonary artery extended out into the finer branches. No emboli or thrombi were seen. About 2 cm. above the aortic valve ring and on the inferior aspect of the arch of the aorta opposite the origin of the left subclavian artery was a patent ductus arteriosus opening into the left main branch of the pulmonary artery just beyond its origin. The ductus was 1 cm. in diameter and the edges were smooth. Since the walls of the aorta and pulmonary artery were closely approximated at this point the ductus was very short (fig. 4). No other congenital anomalies were noted. The atrial and ventricular septa were intact. The right lung weighed 860 Gm. and the left lung 560 Gm. Both lungs were markedly congested in the basal portions and readily oozed fluid upon compression. No infarcts were seen. The liver weighed 1560 Gm. and the appearance of the cut surface was suggestive of passive congestion. The remainder of the examination was not remarkable.

Microscopic examination of the lungs revealed an extensive bronchopneumonia and pulmonary congestion with edema. The larger branches of the pulmonary artery adjacent to the aortic-pulmonary communication were markedly thickened by medial hypertrophy and intimal fibrosis with atheroma formation (fig. 5). Several discrete scars were present in which the medial elastic tissue was replaced by collagenous tissue containing small blood vessels. These scars were similar to those also found in the media of the aorta. Occasional small focal collections of lymphocytes were present in the adventitia. The smaller branches of the pulmonary artery, and particularly the arterioles, showed a striking narrowing of their lumina by concentric intimal fibrous proliferation and reduplication of the elastic layers (fig. 5). No evidence of arteritis or thrombosis with recanalization was seen. Sections of thoracic aorta revealed intimal thickening with atheroma formation, vascular fibrous tissue scars and rare focal collections of lymphocytes in the adventitia. Sections of the right ventricle revealed hypertrophy of myocardial fibers and a moderate amount of fibrous tissue diffusely distributed throughout the muscle fibers in somewhat long strands but occasionally near vessels in fairly dense masses.

Similar scars were also present in sections of the left ventricle. Sections of liver showed central congestion and thinning of central hepatic cell cords with some areas of central necrosis.

Comment. The ductus in this case was very short, the wall of the aorta and pulmonary artery being closely approximated at that point. The gross and histologic evidence of syphilis in the aorta and pulmonary artery must be evaluated. The ductus was probably not a perforated aortic aneurysm since it was in the usual location for a ductus and no ductal remnant was found elsewhere. Further enlargement of the orifice could have been caused by syphilis. There was no histologic evidence that the narrowing of the smaller arterioles was syphilitic in origin. The aortic stenosis was mild and probably produced little functional disturbance.

Discussion

The occasional association of an isolated patent ductus arteriosus with marked right ventricular hypertrophy and an atypical clinical picture has been noted previously. In 1924

Holman[11] discussed the problem and presented 16 cases he had collected from the literature in which right ventricular hypertrophy was present. He pointed out the possibility of a right to left shunt occurring through the ductus and in six of his collected cases there appeared to be clear postmortem evidence that such reversal of flow had been present during life. Since then several reports of similar cases have appeared.[12-18 (case 1), 19] None of these cases, however, exhibited any clear evidence of a reversal of flow through the ductus. In 1944 Chapman and Robbins[20] reported in detail the case of a 37 year old taxi driver who exhibited chronic cyanosis, polycythemia with a packed cell volume varying from 60 to 74 per cent, right axis deviation in the electrocardiogram, right ventricular and pulmonary artery enlargement by x-ray study and an inconstant pulmonary diastolic murmur. The arterial oxygen saturation was 75 per cent. Although not stated in the report, the determination was probably on a femoral arterial sample. Autopsy revealed a huge right ventricle, enlargement and grossly visible arteriosclerosis of the pulmonary artery and a very short ductus 1.2 cm. in diameter. Histologic studies revealed luminal narrowing of the smaller pulmonary vessels which were suggestive of recanalization of vascular thrombi.[20 (figs. 3, 4, 5 and 6)] Five subsequent reports[21-25] have been made of cases in which a right-to-left shunt through the ductus was present but complete physiologic data are available in only one report[23] and in that instance the magnitude of the shunt was small.

It is possible that the number of patients reported in the past do not give a true picture of the actual incidence of these cases, which may be relatively high. Dammann and Sell[19] encountered 15 cases at the John Hopkins Hospital, all of which came to surgery in one year. The examination of reports of large numbers of patients studied by cardiac catheterization reveals several instances of marked pulmonary hypertension associated with patency of the ductus arteriosus.[15, 26, 27, 28, 33] It is possible also that many cases, particularly those with reversal of blood flow, are unrecognized and are erroneously diagnosed as cases of Eisenmenger's syndrome[29 (case 0261), 25] atrial septal defects with pulmonary hypertension and primary pulmonary hypertension. The eight cases reported in this paper were seen in the space of four years in a hospital where, during the same period of time, six cases of Eisenmenger's syndrome were found so that the incidence of these two conditions may be comparable. For these reasons it is important to examine the clinical manifestations of this syndrome so that its correct recognition can be made more frequently.

Clinical Features

Symptoms. The most frequent symptom noted by all patients was the presence of dyspnea on exertion. This was not associated with orthopnea or nocturnal dyspnea except in terminal heart failure. In addition four patients noted a sensation of abnormal weakness or fatigue on exertion described in one instance as "a feeling as if my legs were going to fold up under me." Three patients complained of attacks of substernal pain made worse by exertion and two patients noted episodes of vomiting or nausea.

Physical Findings. In none of these cases was the typical continuous murmur of a patent ductus present nor was there any evidence that it had been present in the past. In all patients the pulmonic second sound was loud and at times accompanied by a palpable shock. In four patients a blowing diastolic murmur was present along the left sternal border which was probably a Graham Steele murmur. In one case (J. J.) the murmur was very loud and accompanied by a palpable thrill. In four cases a loud systolic murmur was present over the pulmonic area and in three of these cases the murmur was accompanied by a palpable thrill. It is of interest that one patient (G. F.) had no audible murmurs and that one patient (J. W.) had only a grade II systolic murmur along the left sternal border.

In the four patients with right to left shunts the arterial blood pressure was normal with a decreased pulse pressure in one case (100/96, 100/70, 120/80, 110/80). No abnormal carotid artery pulsations were noted. In contrast, in the four patients with predominant left to right

shunts, the pulse pressure was distinctly increased (100/60, 95/35, 135/65, 142/64) and prominent pulsations of the carotid arteries were noted in the neck.

X-ray examination revealed in every case a prominence of the pulmonary artery and its branches and enlargement of the right ventricle. Increased pulmonary artery pulsations producing a "hilar dance" was noted in three of the noncyanotic cases and distinct x-ray evidence of left ventricular enlargement was present in two of these cases.

Each of the cyanotic and one of the noncyanotic patients had electrocardiograms which were compatible with marked right ventricular hypertrophy. The other noncyanotic patients had electrocardiograms suggesting hypertrophy of both right and left ventricles.

The catheterization findings are characteristic in the noncyanotic cases and should clearly establish the correct diagnosis. In cases with a reversal of the shunt the diagnosis by cardiac catheterization may be more difficult. The difference in oxygen contents between the right ventricle and the pulmonary artery may be small. In the presence of a prominent degree of functional pulmonic insufficiency the oxygen content of blood samples removed from the outflow tract of the right ventricle may be high and incorrectly suggest the presence of an interventricular septal defect. If, in addition, only femoral blood samples are obtained, the erroneous diagnosis of an Eisenmenger's syndrome may be made. The simultaneous withdrawal of samples from brachial and femoral arteries before and after exercise will prevent this error.

It is of interest that angiocardiography in one cyanotic case (C. P.) failed to demonstrate the right to left shunt through the ductus which was clearly established by the arterial oxygen studies. The volume of the right to left shunt in this case was probably not large enough to enable the contrast media to be seen in the aorta. In G. F. contrast media was seen in the aorta but it was not sufficiently concentrated to demonstrate the ductus. Apparently contrast media may fill the aorta just proximal to the point of insertion of the ductus and in the anterior-posterior projection falsely suggest the presence of an over-riding aorta.[25]

Physiology and Pathology. In the usual patent ductus there is a relatively large flow of blood from the aorta to the pulmonary artery ranging from 2 to 10 liters per minute.[33, 34, 35] This results in an increase of total pulmonary blood flow to levels of 6 to 15 liters per minute. In these cases there is either a normal or only moderately elevated pulmonary artery pressure, the degree of elevation being roughly related to the magnitude of the shunt. This capacity of tolerating even fairly large flows with only slight elevations in pressure is a characteristic of the pulmonary vascular bed and is due to its low resistance to flow.

The most important common physiologic feature of the cases presented in this paper is the presence of a marked elevation of pulmonary artery pressure. This may be due to either an elevation of total pulmonary flow or to an increase in the pulmonary vascular resistance. Inspection of figure 6 reveals no relation between total pulmonary flow and pulmonary artery pressure in these cases. The noncyanotic cases had pulmonary flows no greater than those encountered in the usual patent ductus yet the pressures were markedly elevated. The cyanotic cases had the highest pulmonary artery pressure of the group with the lowest calculated pulmonary blood flows. The uncomplicated patent ductus had relatively normal pressures and demonstrated a roughly linear relationship between pulmonary flow and pressure. The ligation of the ductus in patient E. B., while it lowered moderately the pulmonary artery pressure by decreasing the total pulmonary flow, did not reduce the peripheral resistance of the pulmonary vascular bed, and after surgery the pulmonary artery pressure was still abnormally high. This indicates that the major cause of the pulmonary hypertension is an increase in the vascular resistance of the lung. Calculation of the pulmonary peripheral resistances in these cases indicates that this increase is striking (table 7). Further confirmation of increased pulmonary vascular resistance was obtained by the data on postmortem studies in J. J. in which the kerosene perfusibility was greatly impaired

and the injected specimen revealed a striking obliteration of the smaller branches of the pulmonary artery. In addition histologic studies have revealed marked alterations in the structure of the smaller pulmonary arteries which would obstruct easy flow of blood through these vessels. These data also suggest that this vascular narrowing is anatomic and probably largely irreversible instead of being functional and related to a sustained arterial hypertonus as has been postulated to exist in other varieties of pulmonary hypertension.[31]

It is important to examine briefly the cause of this vascular narrowing. Four general possibilities exist: (1) It is the result of a prolonged increase in total pulmonary blood flow and represents a late complication of the usual patent ductus arteriosus. (2) It is the result of multiple pulmonary emboli probably of small size and occurring in repeated episodes or over long periods of time. (3) It is due to an antecedent acute pulmonary arteritis with subsequent healing and vascular occlusion. (4) It is due to the persistence of the high pulmonary vascular resistance of the fetus into postnatal life.

The first possibility seems unlikely since in none of the cases presented was there a history of a continuous murmur being present at an earlier age and in one case, G. F., cyanosis, and presumably a right to left shunt, had early been present since infancy. Pulmonary vascular lesions are not present in cases of the usual patent ductus[36] and in animals with experimentally produced aortic-pulmonary fistulae, no pulmonary hypertension appears even after several years of observation.[37] Recent reports of patency of the ductus arteriosus persisting into old age have indicated no unusual degree of pulmonary hypertension.[33, 38] The lack of correlation between pulmonary blood flow and pulmonary artery pressure in the patients presented in this paper is evident (fig. 6).

The second possibility seems a good one since it is clear that multiple pulmonary emboli can cause pulmonary hypertension in the absence of congenital heart disease.[41] Experimentally, pulmonary hypertension has been produced by intravenous injection of various substances such as seeds, spores, starch grains, amniotic fluid and finely divided thrombi obtained from the animal's own blood.[42-46]. Histologically an immediate acute arteritis appears with subsequent vascular thromboses and recanalization.[42] The lesions thus produced resemble very closely those encountered in cases of the variety reported in this paper as well as in numerous reported cases of "primary" pulmonary hypertension. The pulmonary vessels in cases D. P., E. B. and J. J. show histologic evidence of recanalization of organized intraluminal thrombi which could have resulted from embolization. The same lesions are described or illustrated in several reports of

TABLE 7.—*Oxygen Consumption, Blood Flow, Cardiac Output, Pulmonary Artery Pressure and Pulmonary Peripheral Resistance in the Six Patients*

Patient	Surf. area-M^2	O_2 cons. cc./min.	Pulm. flow L./min.	Ductus flow L./min.		RV output L./min.	LV output L./min.	Mean Press. PA mm. Hg	Pulm. PR* deter. dynes/cm^5/sec.	Pulm. PR preo. dynes/cm^5/sec.
				L-R	R-L					
V. M.	.79	135 (c)†	4.8	2.3	0	2.5	4.8	62	1032	425
G. F.	1.72	222 (d)‡	4.8	1.9	2.0	4.9	4.8	72	1200	155
E. B.	1.41	326 (d)	9.3	4.8	0	4.5	9.3	78	670	190
C. P.	1.65	251 (d)	3.5	1.4	1.7	3.8	3.5	100	2290	161
W. H.	.60	110 (c)	4.9	2.6	0	2.3	4.9	86	1405	160
J. W., rest	1.90	269 (d)	3.7				3.7	106	2295	140
J. W., ex.	1.90	592 (d)	3.9					137	2810	140
E. B., Postop. rest	1.40	180 (d)	3.9	0	0	3.9	3.9	53	1086	190
E. B., Postop. ex.	1.40	295 (d)	4.5	0	0	4.5	4.5	57	1012	190

* PR = peripheral resistance.
† c = O_2 consumption calculated.
‡ d = O_2 consumption determined.

similar cases.[13, 21, 23, 24, 25] The case reported by Campbell and Hudson[24] is of particular interest since it appeared that a typical continuous murmur with a wide pulse pressure had been present nine years previously and both these features had disappeared at the time of the study three weeks before death. It is a well known fact that pulmonary emboli may occur without striking clinical manifestations, especially if the embolus is small and the lungs are not congested. Certain points, however, are against this attractive theory. Autopsy studies in 13 cases, including reported cases and the three cases in this paper, have revealed only one instance of pulmonary infarction with a grossly demonstrable embolus, and that was of recent origin and occurred during terminal congestive failure.[13] If multiple pulmonary embolization was the basis of the elevation of pulmonary arterial pressure, one would expect some history suggestive of such a process. Such a history is not present either in the eight cases in this paper or in the other reported cases. In several cases it is quite possible that the pulmonary hypertension had been present since infancy, a period of life in which multiple pulmonary emboli would not seem likely to occur. The mere demonstration of recanalization of an organized intravascular thrombus does not establish the diagnosis of embolic vascular occlusion since the thrombosis may be secondary to other processes such as inflammation, for example.

It is possible that in some instances a pulmonary arteritis may be the initial lesion with thromboses and vascular alterations playing a secondary role. The presence of an acute arteritis in case V. M. supports this viewpoint and other cases have been reported with an acute inflammatory process limited to the branches of the pulmonary artery.[47-50] Illustrations of the pulmonary vascular lesions in one report of a patent ductus with pulmonary hypertension show what appears to be a healed arteritis, although this is not mentioned in the text.[21, fig. 3b] In many cases, however, the arteritis may be the initial reaction to multiple emboli since this apparently occurred in the experimental studies of Muirhead and others,[42] or the arteritis may be caused by the elevation of intravascular pressure.

Finally one has to consider the possibility that due to a maladjustment during the neonatal period the equal resistances in the systemic and pulmonary circulations during fetal life persist into postnatal life. It is thought that under certain circumstances the physiologic fall in pulmonary vascular resistance which should take place after birth does not occur, and a persistent elevation of the pulmonary arterial pressure results from it, leading eventually to organic changes in the pulmonary

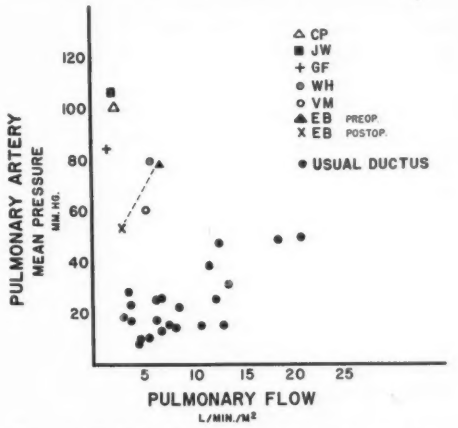

FIG. 6. Relationship between total pulmonary blood flow and mean pulmonary artery pressure in patients with uncomplicated patent ductus and in the patients presented in this paper. Data for the uncomplicated ductus were obtained from patients studied in this laboratory as well as from three papers referred to in the text.[33, 34, 35]

vascular tree. Such a mechanism, initiated by as yet undetermined factors, has been postulated as a condition for survival in certain congenital malformations of the cardiovascular system, such as the Eisenmenger complex,[51] the monoventricular trilocular heart[52] and the syndrome of patent ductus arteriosus with infantile coarctation of the aorta.[53] This mechanism possibly operates in some cases of "primary" pulmonary hypertension occurring in infancy[54, 55] and could well be responsible for some or most cases of patent ductus arteriosus with pulmonary hypertension presented in this report. One could even suggest the possi-

bility that such pulmonary hypertension developing early enough in neonatal life could interfere with the closure of the ductus and thus be the cause rather than the result of patency of the ductus arteriosus.

The striking increase in pulmonary vascular resistance and pulmonary artery pressure is responsible for most of the clinical signs of these cases. The decrease in pressure gradient between the aorta and the pulmonary artery may extinguish the diastolic phase of the continuous murmur and leave only a systolic murmur. In patients with more severe pulmonary hypertension both systolic and diastolic pressures in the aorta and pulmonary artery become equal and no murmur at all may be present.

When the pulmonary artery pressure reaches such levels, a right to left shunt may occur through the ductus, resulting in a reduced femoral arterial oxygen saturation. Exercise appears to increase the difference between the oxygen contents of arterial blood from the upper and lower extremities in the presence of a "reversed shunt" and this may be a useful diagnostic method in cases whose resting femoral arterial saturation is only questionably decreased. Whether the decrease in femoral arterial saturation occurring during exercise is due to an increase in the volume of the right to left shunt or to a fall in the oxygen content of pulmonary artery blood is not known, but it seems likely that both factors may be involved. In J. W., for example, exercise produced a fall of (19.1 to 11.5) 7.6 volumes per cent in the oxygen content of pulmonary artery blood. At the same time brachial arterial pressure rose from 128/76 to 171/86 while the pulmonary artery pressure rose from 130/82 to 168/106, resulting in only a slight increase in the pressure gradient from pulmonary artery to aorta (6 to 10 mm. Hg), and that occurred during diastole only. Here the most important factor causing unsaturation of femoral artery blood during exercise appeared to be the fall in oxygen content of mixed venous blood. Whether this occurs in the similar cases remains to be determined.

The determination of the presence of a right to left shunt through the ductus is important because in the presence of such a shunt surgery appears to be contraindicated.[22, 56] The ductus in such cases may be serving as a "safety valve" keeping pulmonary artery pressure from rising to excessive levels during exercise, or the postoperative deaths that have occurred may be related to the acute pulmonary hypertension resulting from a greatly hypertrophied right ventricle pushing the entire cardiac output through the narrowed pulmonary vascular bed instead of a portion of the flow going through the ductus. It seems clear, however, that in the absence of any demonstrable reversed shunt the ductus can be ligated in the presence of pulmonary hypertension, with gratifying results. The return to normal of an elevated pulmonary flow will lower the pulmonary artery pressure, reduce the work of the right and left ventricles and result in marked clinical improvement. Some pulmonary hypertension will remain, however, since the pulmonary vascular disease has not been affected, as illustrated by the postoperative values obtained in E. B. Whether further gradual improvement will occur remains to be determined.

Summary

1. Eight cases of patent ductus arteriosus associated with pulmonary hypertension have been presented with clinical studies in all cases, cardiac catheterization studies in six cases and autopsy studies in three cases.

2. Four of the patients had conclusive evidence of a right to left or "reversed" shunt through the ductus, and three of these cases presented the clinical picture of chronic cyanotic congenital heart disease.

3. Four cases had no evidence of a right to left shunt but presented an atypical clinical picture with absence of the characteristic continuous murmur and evidence of enlargement of the right ventricle in the electrocardiogram and x-ray. Two of these cases were greatly improved following ligation of the ductus.

4. This study suggests that the basis of this syndrome is an elevation of the anatomic re-

sistance of the pulmonary vascular bed with a resultant increase in pulmonary artery pressure. The cause of this increased resistance is not apparent, but thrombosis with recanalization, and in one instance a diffuse arteritis, has been demonstrated. Clinical evidence suggests that in some cases the disease has been present since birth. No evidence was found suggesting that it was the result of a prolonged elevation of pulmonary blood flow.

5. It appears that surgery is indicated in those cases in which a right to left shunt is not present but that ligation may be dangerous or fatal in instances where a right to left or "reversed" shunt is present.

6. The most important single diagnostic study which will detect the presence of a ductus with a reversed shunt consists of the determination of the oxygen content of simultaneously drawn blood samples from the right brachial and femoral artery at rest and during exercise.

7. Cardiac catheterization is necessary to detect accurately the "atypical" ductus without a right to left shunt, which may be erroneously diagnosed clinically as an atrial septal defect with pulmonary hypertension or "primary" pulmonary hypertension.

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Sumario Español

Ocho casos de conducto arterioso patente asociado con hipertensión pulmonar marcada son presentados con estudios completos de cateterización cardíaca en seis pacientes y estudios de autopsia en tres. Cuatro pacientes tenían evidencia clara de una desviación inversa a través del conducto, tres de ellos presentaban el cuadro clínico de enfermedad congénita cianótica del corazón. Los autores discuten la naturaleza del aumento en resistencia de la red vascular pulmonar que es la base de los cambios circulatorios en estos casos.

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Aging Processes in the Arterial and Venous Systems of the Lower Extremities

By MORTON D. PAREIRA, M.D., FRED P. HANDLER, M.D., AND HERMAN T. BLUMENTHAL, PH.D., M.D.

Wear and tear degenerative patterns of the arterial system of the lower extremities have been studied in an age series. The intensity of these alterations has been correlated with the distribution of the atheromatous plaques and thrombosis as well as with the effective tension at various levels as calculated by Burton's formula. Evidence is presented for the concept that the lipids in atheromatous plaques arise as a product of these degenerative reactions within the vessel wall, rather than by diffusion from the circulation through the endothelial barrier.

IN PREVIOUS reports we have defined aging processes in blood vessels as those alterations resulting from the effects of wear and tear factors which have been operating over a relatively long period of time.[1-6] Specifically, these investigations have dealt with the comparative rates of degeneration, new formation and subsequent calcification of the elastic elements of arteries in various anatomic sites. In general, intimal plaques were observed to occur most frequently in those arteries in which these alterations were most marked along the internal elastic zone, and it was further pointed out that physical factors play an important role in the point of localization and rate of development of these plaques. Thus, the lower portion of the aorta and the coronary arteries show a relatively rapid development of aging processes and a high rate of occurrence of intimal plaques, while the hepatic and pulmonary arteries show atheromata rarely and only a slow and mild progression of elastic tissue calcification. Differences in the rate of development of these changes in elastic elements between Negro and white groups have been studied in comparable segments of coronary, renal, splenic and pulmonary arteries, as well as various portions of the aorta.

From the Departments of Surgery and Pathology, The Jewish Hospital of St. Louis; The Snodgras Laboratory, St. Louis City Hospital; and the Department of Pathology, St. Louis University School of Medicine, St. Louis, Mo.

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Following upon the pioneer descriptive studies of the European founders of pathology, the standard textbooks in this field continue to distinguish three forms of degenerative vascular alterations: atherosclerosis, which is stated to occur primarily in elastic arteries; Mönckeberg sclerosis, which is believed to be principally a disease of muscular arteries; and hyaline intimal proliferation, which is supposed to occur primarily in small arteries and arterioles.[7-9] It has become apparent from our previous studies that no such anatomic distinction can be made. While in young individuals there is a gradual diminution in the concentration of elastic elements in the medial coat of arteries with increasing order of branching from the aorta, these elastic elements are as capable of reduplication, degeneration and calcification in any of these sites as in the aorta or its first order branches. Furthermore, lipids, from which the term "atherosclerosis" is derived, may be found in elastic arteries, muscular arteries, including those of the lower extremities,[10] and small arteries and arterioles.[11]

That physical forces are important in the determination of the intensity of changes in the elastic elements became apparent when it was noted that "rock" and bone formation occur in such branches as the renal and splenic arteries. Similar changes have also been described in the coronary arteries of infants, probably as a result of some disturbance in calcium metabolism.[12-14] The present investigations were undertaken in order to study the role of physical forces in the determination of the intensity of changes in the elastic elements. It seemed

that the vascular tree of the lower extremity would lend itself well to such a study, since the elastic elements in young individuals are sharply defined, a variety of sizes of vessels can be studied and readily measured, and the magnitude of the physical forces exerted upon them can be calculated. The present study, like our previous studies, attempts to relate the frequency and site of plaque formation and thrombosis to the distribution of elastic elements and the intensity of their aging changes. Observations were made on veins as well as arteries.

Material and Method

The major arteries and veins were dissected out of 45 lower extremities; most of these were in extremities amputated at the midthigh region and in each of these a full complement of vessels, as designated below, was obtained. The entire length of the vessels was studied grossly for sites of thrombotic occlusion. Thirty-six of the 45 limbs were amputated because of gangrene resulting from vascular occlusion on an arteriosclerotic basis; the youngest patient whose limb was studied was a diabetic, aged 47. Accordingly, the age of the latter case served as a division point between the group showing marked vascular sclerosis and a smaller group of nine younger individuals whose extremities were amputated because of tumor or trauma. The latter group was utilized in order to study the earlier aging changes.

A full complement of arteries for histologic study consisted of a segment of the popliteal artery at a level of about 1 cm. above the popliteal fold, a segment of anterior and posterior tibial arteries obtained 1 cm. distal to the point of bifurcation from the popliteal artery, a second segment of each tibial artery about 1 cm. above the malleolar line, a segment of dorsalis pedis artery about 3 cm. below the malleolar line, and a segment of digital artery (including skin) about 1 cm. distal to the interdigital web. Specimens of gastrocnemius muscle were taken for a study of its nutrient arteries.

In the case of the popliteal and both tibial arteries transverse and longitudinal sections were studied. In most instances additional sections were taken through plaques or thrombi, when such could be found, between the amputation site and the malleolar line. All specimens were fixed in formaldehyde solution diluted 1:10 with dehydrated alcohol and processed as described in previous reports.[1-6] One section was stained with hematoxylin and eosin; an adjacent section was stained for elastic tissue by the Weigert-Verhoeff method; a third section was microincinerated and studied by dark field illumination for mineral distribution.

In the course of these studies it became apparent that measurement of the internal diameter of vessels would appreciably aid in interpreting the results. Accordingly, such measurements were obtained from the lower extremities of six cadavers, all over 50 years of age.* In no instance was there evidence of occlusive vascular disease as evidenced by thrombosis of any of the vessels included in this series. From these data the internal hydrostatic pressures at various levels were calculated from the Laplace formula $T = P \times R$ as developed by Burton,[17] where T represents the tension, P the blood pressure, R the radius of the artery. The height of the pressures thus determined was compared with the intensity of alterations in the elastic elements as well as the frequency of plaque formation and thrombosis.

Results

Aging Changes in the Arteries of the Lower Extremities

From our previous studies of other arteries, it is apparent that in the newborn the internal elastic lamella of all arteries lies against the endothelial lining. An examination of the lower extremity vessels in several stillborn infants resulted in the same finding. The external elastic lamella consists of several rows of thin, elongated elastic fibers. Microincinerated sections of all of these arteries showed only a nuclear distribution of calcium.

Popliteal Artery. By the age of 20, changes from the above basic pattern are already apparent. A thin layer of collagen of irregular thickness separates the endothelium from the inner elastic zone. The latter consists of several parallel wavy fibers, from which finer filaments extend into the media as well as into the intimal layer of collagen; this is accompanied by deposits of calcium along these elastic elements (fig. 1). With increasing age the subendothelial layer of collagen becomes progressively thicker and contains a greater number of elastic filaments; the latter appear to break down into shorter filaments and fine granules which take the elastic stain. Elastic tissue extensions of similar character are also found in the media in progressively increasing amounts, and calcification in the media also becomes progressively more intense. As this process con-

* We are indebted to Dr. W. F. Alexander of the Department of Anatomy, St. Louis University School of Medicine, for these measurements.

tinues there is a coalescence of elastic elements along the inner elastic zone as well as through the media. With increasing collagen deposition, or with organization of a thrombus (fig. 4), elastic elements may be replaced by ingrowths of fibroblasts. Finally, calcification may become so severe that bone formation results (fig. 3). Continuity of elastic elements with bone has usually been present in this study, the inner margin of bone usually being covered by the internal elastic zone which contains foci of intense calcification (fig. 2).

Tibial Arteries. Both anterior and posterior tibial arteries show essentially the same progression of aging changes as described above. In these arteries, as well as in the popliteal, typical atheromata can be found. These contain cholesterol slits surrounded by hyaline tissue and occasional giant cells and macrophages. As in the case of the aorta, plaques may become so large that pressure atrophy of the media ensues, with resulting disappearance of many elastic elements (fig. 5). With thrombosis and recanalization, a new inner elastic membrane frequently forms just beneath the new endothelial lining. This new internal elastica undergoes duplications, and wavy elastic fibrils extend into the thick organizing fibroblastic layer. There is apparently no continuity between these newformed elastic elements and those in the original vessel wall. The vessel wall, however, continues to show a thick subintimal layer rich in elastic elements; thickened, duplicated elastic lamellae, and numerous fragments, filaments and granules of elastic material are scattered through the media. Many such arteries show "rock" formations extending from the internal elastic zone to the adventitia, and transitions from rock to bone formation are encountered more frequently in tibial than in popliteal arteries. The direct continuity of elastic tissue with these areas of rock formation is easily discernible. Calcification of elastic elements goes on in the vessel wall proper as well as in newly formed elastic tissue about the newly formed channels (fig. 3).

Dorsalis Pedis Artery. The aging changes in this vessel are qualitatively similar to those described above, but progress at a much slower rate. Duplications of the internal elastic lamella are much less pronounced at about the age of 20 and there are fewer elastic filaments in the media. Subendothelial collagen deposition is also not as marked, but even in these, elastic filaments may be seen. Actual rock formation was encountered in only one subject, an individual 90 years of age (fig. 6).

Digital and Muscular Arteries. Subendothelial collagen deposition occurs quite late in vessels of the caliber encountered in muscle septa and in the digital vessels. Duplications of the internal elastic lamella are seen very rarely, but fenestrations of the elastic membrane are frequent (fig. 7). The media only rarely shows fine elastic filaments. A thin line of calcium usually outlines the internal elastic membrane in incinerated preparations, but the media calcium remains nuclear in distribution in aged individuals.

Aging Changes in the Veins of the Lower Extremities

Observations were limited to the popliteal and tibial veins and, in general, the findings correspond to those described by Lev and Saphir.[16] Endophlebohypertrophy, consisting of a proliferation of collagenous connective tissue and the appearance of fibrils of elastic staining material in the intima, appears even in specimens from young subjects; these veins also show collections of elastic fibrils between muscle fibrils in the media. An early deposition of calcium along these elastic elements is observed in incinerated specimens. In older individuals there is disruption of the internal elastic lamella and of many elastic fibrils in the intima and media. Resulting from this there are fragments, filaments and granules of elastic staining material in both layers, accompanied by progressively increasing calcification of these elements. Phlebosclerotic plaques are numerous in veins of older individuals, and contain disrupted elastic elements and deposits of calcium (fig. 8). As we have noted in arteries, and as also observed by Lev and Saphir,[16] elastic fibers are abruptly interrupted at the margins of areas of calcification. However, the use of incinerated sections has permitted the additional observation that calcification first occurs along elastic elements, although the latter may subsequently

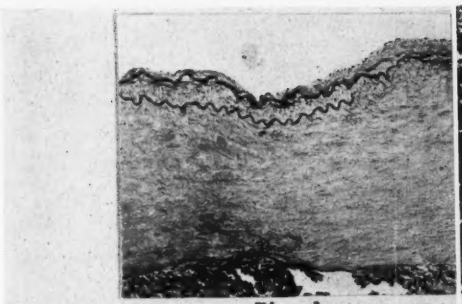

Fig. 1a

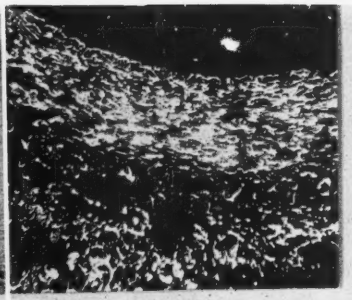

Fig. 1b

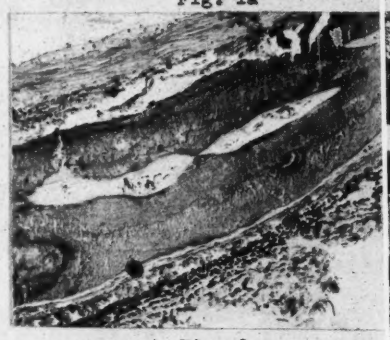

Fig. 2a

Fig. 2b

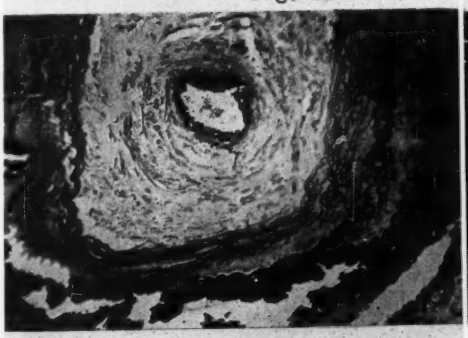

Fig. 3a

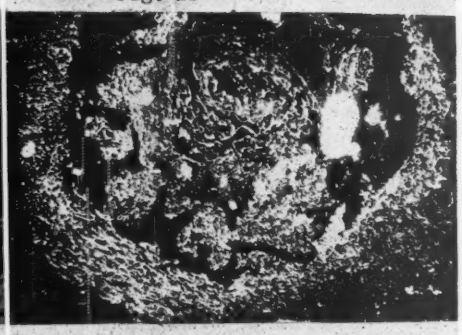

Fig. 3b

FIG. 1. Popliteal artery; 21 year old male. Figure 1*a* illustrates the early duplication of the internal elastic lamella with fine granular elastic staining material between the two wavy fibers as well as between the upper fiber and the endothelial lining. Granular elastic material can be seen along the left half of the microphotograph deep in the media. Figure 1*b* shows calcification of the duplicated elastic lamella and of the media; some of the latter is not limited to elastic elements. (× 66)

FIG. 2. Popliteal artery; 63 year old male. Both 2*a* and 2*b* show bone formation replacing the media. In 2*a* a thin elastic band courses along the inner surface of the bone, and elastic fibrils and granules are present in the intima. (Compare with fig. 3 which probably represents an earlier stage of this process.) Calcium ash corresponding to the elastic elements and the bone are present in 2*b*. (× 66)

FIG. 3. Anterior tibial artery; 90 year old male. Figure 3*a* shows a recanalized thrombus with an elastic lamella about the newly formed lumen. This lamella shows duplications and some granulation. Elastic fibrils are also scattered through the fibrous tissue between the lumen and the original inner elastic zone. The black area at the bottom of the microphotograph is a mass of calcific material typical of Mönckeberg sclerosis, but its contiguity and continuity with elastic elements as well as its affinity for elastic stains indicates elastic extension into the media. Figure 3*b* shows deposition of white mineral ash along the newly formed elastic elements as well as heavy calcific deposits in the media, the latter resulting in some tearing of the section. (× 66)

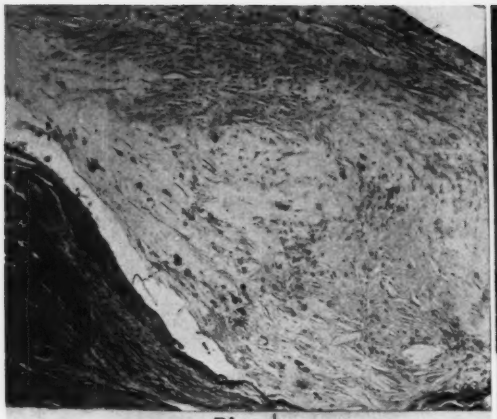

Fig. 4

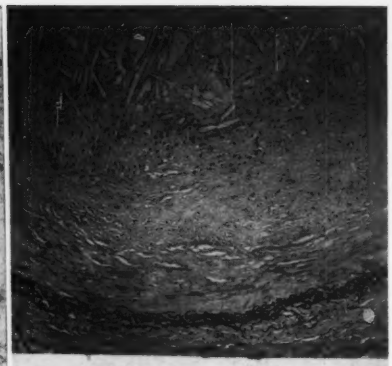

Fig. 5

Fig. 6a

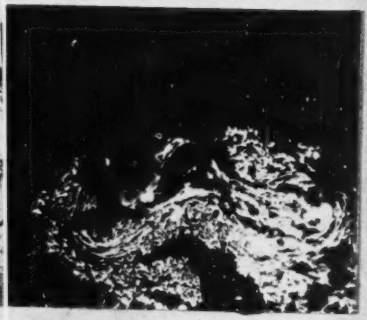

Fig. 6b

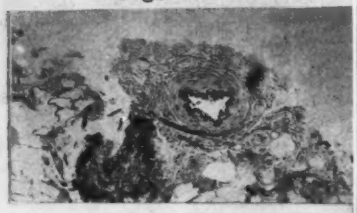

Fig. 7

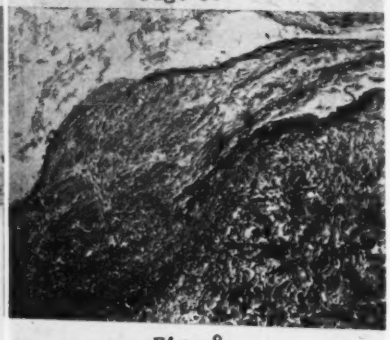

Fig. 8

FIG. 4. Popliteal artery; 75 year old male. The media of this artery is in the lower left hand corner. It is composed of densely packed elastic elements similar to those seen in figure 3. The identity of the internal elastic lamella can be made out as a continuation of the inner margin of the media towards the right. This area was so heavily calcified in the incinerated specimen that fragmentation resulted in a complete loss of anatomic relationships. The intima is markedly thickened and composed of fibroblasts in a basophilic matrix. Cholesterol slits are present in the lower right hand corner of the intima. A newly formed thin elastic lamella lies immediately beneath the endothelial lining. (× 66)

FIG. 5. Anterior tibial artery; 70 year old male. A large atheromatous plaque has resulted in replacement by fibrous tissue of intima as well as media, including elastic structures. Numerous cholesterol slits are present in the upper part of the photomicrograph. (× 66)

FIG. 6. Dorsalis pedis artery; 90 year old male. Figure 6*a* shows marked thinning of the wall and several foci of calcification in continuity with elastic elements. Figure 6*b* shows dense white mineral ash particularly heavy in the zone corresponding to the black portion in 6*a*. Note lack of elastic material in a relatively thin intima. (× 66)

FIG. 7. Digital artery; 69 year old male. The artery has a relatively "youthful" appearance despite the age of the patient. There is negligible intimal thickening and only slight fragmentation of elastic elements. (× 66)

FIG. 8. Posterior tibial vein; 69 year old male. Note numerous elastic fragments, filaments and granules through all layers of the wall, as well as a plaque-like elevation of the intima. Incinerations of such specimens show extensive calcification. (× 66)

disappear either in a calcific mass or by replacement by collagenous connective tissue.

Furthermore, we have been able to corroborate the observation of Lev and Saphir[16] that at the point of contact of artery and vein no plaque is formed, but rather they are found to the sides of indentations produced by such contact. Where artery and vein are contiguous however, there is a disruption of elastic elements of the external lamellar zone and calcification of the media.

The Relation of Hydrodynamic Stresses to Aging Changes in Blood Vessels

Several interesting associations can be made from the data shown in table 1. Those arteries which show the most intense calcification in incinerated sections also show the highest incidence of plaque formation. The most severe calcification was found in the popliteal artery, in which there was also the greatest frequency of plaque formation; in both instances this was followed by the tibial arteries and then the dorsalis pedis artery. The digital arteries and the nutrient arteries of muscle showed less than 1 plus calcification even in aged individuals and no plaques were observed in these vessels. This same order obtains when the hydrostatic tension, as calculated by the formula of Burton,[17] is compared with the incidence of plaque formation and with the intensity of calcification. On the other hand, thrombi were most frequently found in one or the other tibial arteries despite the higher incidence of plaques, greater intensity of calcification and higher hydrostatic tension in the popliteal artery.

TABLE 1.—*Severity of Aging Changes as Related to Hydrostatic Tension*

Artery	Number of Cases	Per cent with plaques	Per cent with thrombi	Average calcification	Internal diameter*	Hydrostatic tensions†
					cm.	*dynes/cm.*
Popliteal	36	78	30	3.4+	0.49	26,480
Tibials (combined)	35	73	70	2.7+	0.22	11,440
Dorsalis Pedis	29	31	32	1.7+	0.14	6,370
Digital	28	0	0	0.6+	0.04	1,820
Muscular	27	0	0	0.4+	0.02	800

* Figures obtained by measurements on extremities of 16 cadavers.

† Calcuated from formula of Laplace, as applied by Burton[17]: T (Tension) = P (Blood Pressure) × R (Radius of artery).

Discussion

In his original study Mönckeberg[15] described the changes in the wall of the arteries of the extremities as calcification which could occur independently of "atheromatous disease." This view is still held by many present-day investigators. However, it has become increasingly clear as our investigations have progressed that calcification predominantly occurs in or along elastic fibers, and that the changes of this type along the internal elastic lamella constitute the earliest phase of plaque formation and form an integral part of the atheroma. The appearance of lipids is a late phenomenon, whether in the coronary artery, abdominal aorta, or the popliteal or tibial arteries of the lower extremities.

Further evidence that these elastic tissue changes and the formation of atheromatous plaques are not independent phenomena lies in the fact that there is a close correlation in the degree of severity of these processes in a given artery. Calcification of elastic elements in the coronary artery of the Negro progresses more slowly than in white individuals, and the incidence of coronary artery atheromatosis and thrombosis in the Negro is considerably lower.[5] The elastic tissue changes progress extremely slowly in the pulmonary artery of both races, and it is well known that atheroma formation is a relatively rare phenomenon in the pulmonary arterial system.[6] Atheromata do appear in the arteries of this system when pulmonary hypertension, which leads to accelerated elastic tissue alteration and calcification, develops. Similarly, the frequency of atheroma formation can be closely correlated with the severity of elastic tissue calcification in the various segments of the aorta, and in the splenic, hepatic and renal arteries.[3, 4]

The changes described in the present investigations are qualitatively similar to those previously described in other major arteries and differ only quantitatively. The increased severity can be accounted for in large part by the greater hydrostatic tension obtaining in

the popliteal and tibial arteries than in those occupying a more cephalad location in the upright human.

The reactions produced by hydrodynamic stresses may be most easily studied in vessels normally operating at relatively low pressures, such as veins and the pulmonary arterial tree. As Lev and Saphir[16] have pointed out, the first reaction produced by stresses in veins is endophlebohypertrophy; intimal hypertrophy is also the earliest reaction in the pulmonary arterial tree, where it normally occurs in the third or fourth decade as compared with the second decade in arteries operating under higher tensions. In both veins and arteries the continuous application of hydrodynamic stresses operating progressively with age results in a disruption of elastic elements and calcification. In vessels functioning at low pressures and relatively low hydrostatic tensions these elastic tissue changes progress slowly and lipid deposits either do not occur, or are observed only in very aged individuals, while in arteries operating at higher pressures and hydrostatic tensions these changes occur with greater rapidity, and plaque formation, including the deposition of lipids, is observed with greater frequency.

Hormonal factors may also play a part in these changes. Wells[18] has pointed out that epinephrine is the most important of these. Repeated injections of epinephrine into animals results in the appearance of a marked atheromatous degeneration of the aorta with calcification. This was first observed by Josué and later by Erb, Fischer, Gouget, Loeb and Githens and others.[19] These changes resemble most closely those seen in the arteries of the extremities. They may not be due to the heightened blood pressure, since simultaneous injections of substances that depress the blood pressure do not prevent the atheroma from developing, while the injection of certain other substances that elevate blood pressure does not cause atheromata. On the other hand, the slow injection of epinephrine, regulated so that there is an increase in the blood content without significant rise in blood pressure, fails to produce arteriosclerosis.[20] Thus, while the histologic changes produced in arteries by epinephrine are well known, the mechanism inducing these changes remains unsolved.

These investigations of vessel wall changes induced by epinephrine indicate that calcification appears predominantly in the elastic tissue, but that there is also calcification of the degenerating smooth muscle of the media. We have observed and reported this calcification pattern in the splenic and renal arteries. It was also found present to some degree in the popliteal and tibial arteries in the present investigations; however, because of its unimportance in the formation of intimal plaques, consideration was not given to this finding in describing our results.

It has become apparent in recent years that the opinion that atherosclerosis is a lesion solely of the elastic arteries is an erroneous one. Several investigators have observed a high incidence of atheromatous plaques in amputated lower extremities, and our results are in agreement. This being the case, one may wonder why thrombosis with ensuing gangrene is not as frequent in arteries of the lower extremities as in the cerebral and coronary arteries. That the incidence of gangrene in the lower extremity is much less than the incidence of cardiac or cerebral infarction could rest, in part, on the ability of the former to develop more effective collateral circulations. However, it is strikingly illustrated by our observations that the caliber of those vessels of the lower extremities which operate under high hydrostatic tension and show frequent atheromatous plaques is larger than that of the coronary or cerebral arteries. It would be expected that atheromatous plaques would be increasingly more conducive to thrombus formation as the vessel in which they resided became progressively smaller. Our observations indicate that whereas the magnitude of atheromatosis in the arteries of the lower extremity diminishes progressively as the caliber of the vessels diminishes, it is in the tibial arteries that the highest incidence of thrombus formation appears. Thus it seems that the relation of vessel caliber and degree of atheromatous change is an important factor in thrombosis. Thrombosis is uncommon in the femoral artery where atheromatosis is marked but vessel caliber relatively large, and in the digital artery where vessel caliber is relatively small but atheromatosis is minimal. The statement of Edwards[10] that "thrombosis of the

tibial arteries does not usually lead to gangrene unless the popliteal artery is already occluded by atheromata" is not supported by our observations.

Summary

These investigations consist of a study of the arterial tree of 45 lower extremities, 36 of which were amputated for arteriosclerotic gangrene. The severity of the elastic tissue-calcium changes is correlated with the incidence and severity of atheromatous plaque formation at various levels, and with the hydrostatic tensions operative at those levels.

It is concluded that the medial changes, particularly those along the inner elastic zone, do not differ qualitatively from similar changes observed in elastic arteries and that they bear an intimate relationship to the formation of atheromatous plaques. The concept of independent intimal and medial changes in muscular arteries does not appear to be a valid one, and the term "Mönckeberg sclerosis" is, therefore, misleading.

Sumario Español

El deterioro y desgaste degenerativo del sistema arterial de las extremidades bajas ha sido estudiado en una serie de edades. La intensidad de estas alteraciones ha sido correlacionada a la distribución de placas ateromatosas y de trombosis al igual que a la tensión efectiva a varios niveles según calculada por la formula de Burton. Evidencia se presenta a favor del concepto de que los lípidos en las placas ateromatosas se originan como un producto de estas reacciones degenerativas dentro de la pared vascular, más bien que por difusión de la circulación a través de la barrera endotelial.

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Studies Made by Simulating Systole at Necropsy

II. Experiments on the Relation of Cardiac and Peripheral Factors to the Genesis of the Pulse Wave and the Ballistocardiogram

By Isaac Starr, M.D., T. G. Schnabel, Jr., M.D., and R. L. Mayock, M.D.

This paper describes results obtained during the last three years with special emphasis on those secured since the development of the technic which permits us to employ compatible blood as perfusion fluid. Using the method of paired experiments, data have been obtained on the effects on the pulse wave and the ballistocardiogram which follow changes in the total energy of the simulated systole, changes in the way that energy is applied during the systole, changes in resistance as measured by diastolic pressure, and differences in the amount of arteriosclerosis present in various subjects.

IN a previous communication[1] a preparation was described in which water or salt solution was injected into the aortas and pulmonary arteries of cadavers at necropsy while the ballistocardiograms and arterial blood pressures were recorded. This first report was based on 91 simulated systoles in six cadavers, all made by injecting the fluid into the great vessels by pushing home the syringe plungers by hand, or by striking them with a mallet guided by hand.

After this experience, enlarged support from the United States Public Health Service permitted us to improve greatly certain parts of our apparatus until we became able to simulate systole by injections into the great vessels initiated by a known energy. We thus became able to vary both strength and character of the simulated "systoles," to duplicate each kind of "systole," and so to study the varying effects of similar "systoles" made under a wide variety of physiologic conditions. So the improvements in our technic permitted studies of a quantitative type impossible to secure by our former method of injecting by hand. Also the acquisition of two Lilly manometers permitted us to secure curves of both aortic and peripheral blood pressure simultaneously, which at once opened a new field of investigation concerned with testing the accuracy of older methods designed to estimate cardiac output from pulse pressure and pulse wave velocity, and with creating better methods for this purpose. Finally we learned how to use compatible blood instead of water for both filling the vessels and injecting into them, a change long delayed because of our fears of the increased technical difficulty it might entail, but which actually made the experiment easier to conduct and led to great improvement in the "normality" of the results.

With these improvements in both apparatus and technic it became evident that in our cadaver preparation we had a unique means of performing many types of physiologic experiments concerned with such fundamental aspects of cardiac function as output, force, work, and power, which could be calculated dynamically from our curves with an accuracy not as yet attained on living men or animals. So we found ourselves able not only to devise rough methods of estimating these important cardiac functions from simple measurements

From the Department of Therapeutic Research and from the Robinette Foundation, Medical Division, of the Hospital of the University of Pennsylvania, Philadelphia, Pa.

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which could be made in the living, but also to test their accuracy in our preparations. Also in the course of this work many observations of physiologic interest were made on the genesis of the pulse wave and its transmission down the aorta.

Our experience, since the experiments described in the last publication,[1] now consists of 305 simulated systoles secured on 24 cadavers, of which 65 systoles in six cadavers were done with blood and the balance with water as the perfusing fluid. As a result the data of interest have proved to have a bulk not possible to compress into one paper, so we plan to start a series of presentations by this communication which is concerned chiefly with our apparatus and technic, with a description of experiments made to test our apparatus, our methods and the "normality" of our preparations; and with certain general features of our experimental results which can be expressed in simple terms. Data requiring more advanced mathematic analysis will appear in subsequent communications.

Apparatus

Changes from our previous apparatus were as follows. The new *ballistocardiograph* used was made by the Technitrol Company[2] and was a high frequency, undamped table of the type long used in this laboratory. A calibrating device with a weight of 280 Gm. was built into it. This instrument had a vibration frequency of 20.5 cycles per second when unloaded, of 12.7 per second when loaded with 100 pounds of iron bars, of 10.8 cycles per second when loaded with 170 pounds of iron bars.

Blood pressures were recorded through small plastic catheters[3] connected with two *Lilly capacitance manometers*[4] also made by the Technitrol Company.

Mirror galvanometers (Hathaway type 0-51) were used to record both blood pressure and ballistocardiogram. Three light sources were zirconium arc lights made by Western Union Telegraph Company, used with a power supply described as C.A.L. type, B 25, made by George W. Gates Company. The galvanometers, light beam sources, slits and lenses were set up on a rigid stone table. The camera film was run with a speed of 5 cm. per second in most experiments.

Apparatus for simulating systole is shown in figure 1. The axle of the swinging mallet was screwed into a collar surrounding the mine jack and it could be set at any height by a set screw.

The wooden mallet weighed 15.5 pounds and the head was 20 cm. in diameter. To lengthen the radius of rotation an iron pipe was fitted over the wooden handle and extended beyond it. To obtain "systoles" of normal duration, ejection velocity and cardiac output, 30 pounds of iron bars were added to the back face of the mallet and fixed there

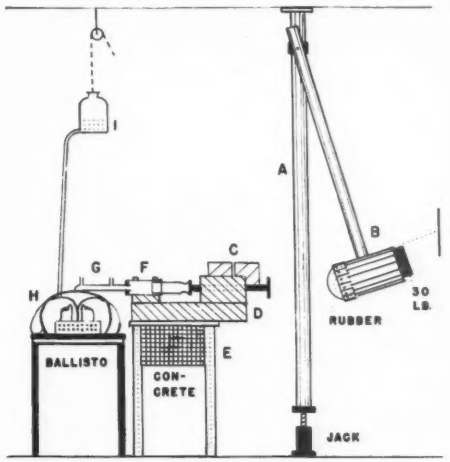

FIG. 1. General setup of apparatus: viewed from the subject's feet. A: The "mine jack," for supporting the axis of the swinging mallet. B: Swinging mallet, weighted and padded, held in cocked position by a chain with a thread link. C: Slit for light beam for recording position of syringe pistons, attached to metal piston, and projecting upward through split cylinder. D: Syringe holder and split cylinder for metal piston, and common base bolted to weighted table. E: Weighted table, with concrete block built into head. F: Nearest syringe, the second syringe immediately behind it does not appear. G: Horizontal and beginning of vertical limbs of nearest glass cannula with side tubes for venting bubbles and filling syringe; the second cannula immediately behind does not appear. The plastic tubes connecting with the side tubes, and their pinch cocks are not shown; nor is the perfusion bottle which provides fluid for displacing bubbles and filling syringes. H: Cadaver, with feet towards the reader, lying on ballistocardiograph, with heels against the foot plate. I: Perfusion bottle for diastolic pressure, connected with cannula in femoral artery. Its elevation can be adjusted by a cord passing over a pulley attached to ceiling.

tightly by chains and turnbuckles. The length from axis of rotation to the bottom of the mallet head was 163 cm. The center of mass was located 132 cm. from the axis. The total weight of mallet, handle, extra weight, rubber and fittings was 58 pounds. When swinging freely from its axis the vibration period was 1.9 second. After striking the metal

piston and driving in the syringe piston, the mallet came to rest at or near its rest point.

The striking surface of the mallet was heavily padded with thick sheets of sponge rubber cut into circular disks and held to the mallet by the flange of a movable sheetmetal collar. The amount of padding on the mallet was varied, and in some experiments a sponge rubber pad was also fastened to cover the handle of the metal piston struck by the mallet. Some of the disks used were of red sponge rubber, 1 cm. thick, and others were of white sponge rubber, 2.5 cm. thick; the pad for the handle was of red sponge rubber, 3.5 cm. thick. Various combinations of these disks were used. An idea of their elasticity can be obtained by the data in table 1 which records the amount of compression caused by the end of a 4 pound iron bar, its surface of contact being a square 1¾ inches on each side, placed on the various combinations of rubber disks piled on the laboratory table.

The *injection apparatus* has been modified only slightly from that described in the previous communication.[1] A ratchet was added to prevent the syringe pistons from being forced backward when "systole" was over. The original cannulas have been divided into two parts by cutting the second limb and then closely approximating the ends by a rubber connection. This improvement permitted rotation of the horizontal third limb on the vertical axis of the second limb and allowed a great improvement in the proper fitting of the cannulas into the heart of each subject. The arrangement can be more easily seen in figure 2 than described.

TABLE 1.—*Compressibility of the Padding Used*

Combination	Rubber used	Compression caused by a 4 lb. weight resting on a square surface 1¾ in. each side
1	2 red disks	0.2 cm.
2	2 red disks, 2 white disks	2.8 cm.
3	2 red disks, 2 white disks and pad	4.0 cm.
4	2 red disks, 4 white disks and pad	4.5 cm.

A small glass "U" tube water manometer was used to keep track of pulmonary diastolic pressure.

The blood used as perfusing fluid was of group "O" and had been discarded from the hospital blood bank as unfit for human use, usually because it had been drawn over one month previously. It had been preserved in the refrigerator from the time it was drawn. About 6 liters were required for the usual experiment.

Tests of the Apparatus

The table of the Technitrol instrument used in these experiments weighed but 27 pounds and so was somewhat lighter than that of our original instrument. To assure ourselves that there was no difference in results we tested three normal subjects repeatedly using the new instrument and our

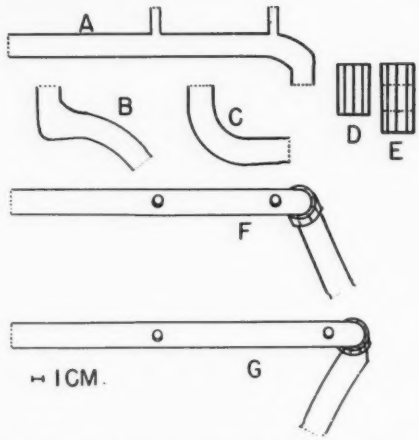

FIG. 2. Diagrams of aortic and pulmonary artery cannulas. A: First part of the glass aortic cannula viewed from the side. The first part of the pulmonary artery cannula is similar but somewhat longer. During an experiment the end shown at the left is attached to the syringe. The side tubes are shown but not the plastic tubes and clamps which close them during an experiment. B: Second part of cannula for insertion through right ventricle into pulmonary artery where it is tied in place, and then attached to the first part. C: Second part of cannula for insertion through left ventricle into aorta where it is tied in place and then attached to the first part. D: Rubber connection for attaching the two parts of a cannula when the chest is narrow, and the glass ends of the 2 parts can be approximated without distortion. E: Example of one of a number of connections containing different lengths of glass tubing used when the heart is deep in the chest. The increased length permits the 1st part of each cannula to lie snugly on the chest wall without the cannula tips distorting the position of heart or great vessels, while the ends of the glass tubes are closely approximated within the rubber connections. F: Aortic cannula, both parts connected, as viewed from above. The tip is at an angle often found during an experiment. In every experiment this angle is adjusted to conform with the position of the heart in the body. G: Pulmonary artery cannula, both parts connected as seen from above. The tip is at the angle found in most hearts during an experiment. During the experiments the first parts of the two cannulas lie side by side. The tip of the pulmonary artery cannula in the right ventricle curves over and crosses the tip of the aortic cannula lying in the left ventricle. G and F lie close alongside each other during an experiment.

old machine alternately. We were not able to detect any difference in the records secured by these two instruments.

The injection apparatus was tested, in the absence of the cadaver, by attaching the tips of the aortic and pulmonary cannulas, through suitable curved glass connectors, to vertical glass or rubber tubes of the same internal diameter as the cannulas (2 cm.). One of these tubes reached to the ceiling and both were long enough to contain columns of water supplying a pressure against the cannula tips the equal of any diastolic pressure secured in the clinic, and also to contain the extra amount which flowed in at systole.

A great deal of experimenting was done using rubber tubes of varying thickness, and air chambers attached to side tubes located near the cannula tips, to allow us to get stroke volumes, and injection curves with contours similar to those secured on the cadaver experiments after similar systolic blows.

From the rise of the columns of water in the vertical tubes the work performed on the fluid by any systolic blow could be readily calculated. Figure 3 gives the work performed in relation to the energy of the blow in four experiments. These experiments were made under widely different conditions of "diastolic pressure" and elasticity of the system, and their divergence from one another is due to this. But the results of each experiment, taken by itself, are well represented by regressions arbitrarily drawn through the origin. Close inspection shows that the true regressions are more probably slightly curved with a downward concavity and that they probably impinge on the base line to the right of the zero point. This is certainly to be expected, the large loss of energy from friction increasing as the blow increased, while a very small blow may not be sufficient to overcome the frictional forces and perform work beyond the syringes. But despite this likelihood the results show clearly that within the limits of our experiments we will not go far wrong if we consider the effect produced on the circulation to be directly proportional to the energy of the blow for any single set of conditions.

Conduct of the Experiment

Although the experiment was conducted much as before,[1] some important improvements must be described. The sternum was sawed through the midline, its halves forced apart by a steel rib retractor of the gear and ratchet type. The pericardium was opened in the midline. Using great care, a passage around the base of the pulmonary artery, and another around the base of the aorta was cleared by blunt dissection, and loose ligatures were passed around these vessels. The left ventricle was incised near the apex of the heart, and the tip of the detached third limb of the aortic cannula was inserted through the chamber into the aorta and tied in place. The right ventricle was then incised at its tip away from the pulmonary artery, and the tip of the detached third limb of the pulmonary cannula was passed through this chamber and tied into the base of the artery. Great care was used to connect the cannulas so that there was no traction on or distortion of the cardiac anatomy and the first limbs lay on the skin surface without being forced into that position.

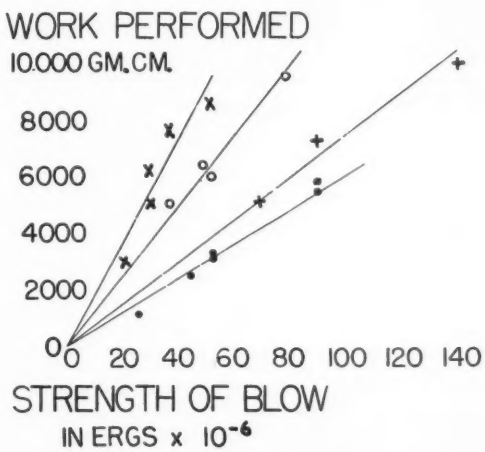

Fig. 3. Relation of energy of blow to work performed. A test of our apparatus. In this figure and in figures 5 and 6 the numbers of the horizontal axis indicate the strength of the blow in ergs. Those unfamiliar with these units may need to be reminded that 1 erg is a very small quantity. Thus if the recorded symbol is over the figure 30 on the X axis, the ergs of the blow would be 30 × 1,000,000 or 30,000,000 ergs. Thus, in these figures any value on the X axis × 10^6 equals the ergs of the blow; or any number equals ergs × 10^{-6}.

In the experiments work was measured by attaching vertical tubes to the tips of the aortic and pulmonary artery cannulas in the absence of a cadaver, and measuring the rise of the fluid column. Results secured under the same set of conditions are shown by the same symbol. The regressions shown have been placed arbitrarily and they are not the calculated best lines.

The blood used for perfusion was warmed in a water bath to about 100 F. just prior to the experiment, thoroughly stirred, and poured through gauze into the large perfusion bottle. The aorta was washed free of clots by allowing blood to flow into the femoral artery and out the aortic cannula, where it was caught in a beaker.

The free ends of the glass cannulas were now attached to the two syringes and bubbles carefully removed from the system by venting them through

the side tubes of the cannulas while blood and saline were allowed to run in. The syringes were then filled to the 100 cc. mark, or near it.

A femoral artery was punctured with a number 21 needle; a small plastic catheter attached to a manometer was threaded through its orifice and passed up the aorta to the top of the arch; the needle was then withdrawn from the vessel wall leaving the tube in place. Using a second needle and puncturing just below the first puncture, a second plastic catheter was inserted into this artery for a few centimeters, and this needle was likewise withdrawn.

The mallet was now "cocked" by drawing it back until a stick of known length could be inserted between the table and the mallet head. The mallet rested on the stick until it could be supported from

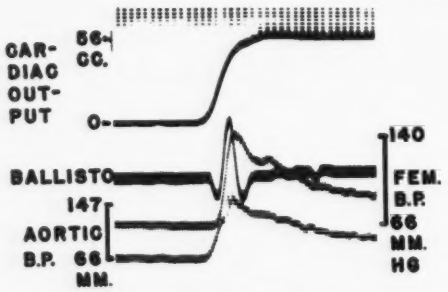

FIG. 4. A typical record of a simulated systole. Systole number 2 of subject H. Z. Upper record is time record; smallest interval, 0.04 second. Second record is record of syringe piston; its calibration is given on the left. Third record is ballistocardiogram; its calibration is not shown. Fourth record is blood pressure recorded in femoral artery; values derived from its calibration are given on the right. Lowest record is blood pressure recorded in aortic arch; values derived from its calibration are given on the left. The reproduction is one-half actual size.

behind by a chain and turnbuckle joined by a link of thread. The turnbuckle was tightened until the stick dropped to the floor, leaving the mallet in a known position and cocked for the blow. Pulmonary diastolic pressure was read on the manometer and adjusted downward if it was above 10 mm. Hg, and lastly the position of the syringe pistons was read from the syringe scale.

All now being ready the room lights were extinguished. The clamp was opened and blood flowed into the femoral artery from the perfusion bottle. When the beams indicated that diastolic pressure had reached a plateau, the cameraman said "Go" and started the camera. The inflow tube of the femoral perfusion of blood was then clamped, and the thread link was burned through as soon as possible, allowing the mallet to drop and force in the syringes. As soon as the resulting impacts and pressure changes were over, the ballistocardiogram was calibrated. The blood pressure base lines were next recorded by opening the side tubes of the manometer heads to the air. Reading the final position of the syringe plungers finished the run. It should be noted that the syringes did not expel all the blood in them; indeed, if either piston struck the end of its barrel the run was discarded.

The syringes were now refilled; changes were made according to the requirements of the next experiment; the mallet was cocked once more and the next "systole" run off immediately. We averaged 13 "systoles" to each cadaver. Once set up, the series required only a short time to complete.

Tests of the responsiveness of the Lilly manometers were made at the beginning, and at the end of each series of experiments by lightly tapping the ends of the small plastic tubes with the finger. We assured ourselves that the responses of the beams were almost instantaneous before proceeding, and sought for bubbles to eliminate if this were not the case. Tests for alignment of the beams were also made.

The manometers were calibrated twice, always at the end of the experiment and usually after the second "systole" by inserting pressures of 50, 100, 150, 200 and 250 mm. by the bulb of an ordinary mercury blood pressure manometer, and photographing the position of the beams. The agreement between the two calibrations was always excellent and the slope was nearly linear.

At the conclusion of the run the heights of the manometer heads above the table were measured. The position of the tip of the aortic pressure catheter was verified and both arterial catheters were withdrawn after marking the point at which they pierced the vessel wall. Their length within the vessel lumen was then measured, so that the distance traversed by the pulse wave passing between the tips could be obtained by difference. The thickness of the chest was recorded by measurement of the height of the sternum above the table; one-half this distance above the table was used to locate a level to which the pressures were referred.

The necropsy was now completed in the usual manner, the pathologist giving special attention to the great vessels from which several pieces were taken for section, and measurements of diameter made at various levels.

Measurement of the Records and Calculations

A typical record of a single "systole" is shown in figure 4. For the results reported in this paper we measured by a millimeter rule placed directly on the photograph using the edge of the time record as base line. All the records secured with blood as perfusion fluid were remeasured and recalculated about six months after the original measurements and in ignorance of the original findings.

The measurements of the ballistocardiogram were corrected by the calibrations of that instrument so that amplitudes recorded in the tables represent those which would have been found if a force of 280 Gm. had displaced the light beams 1 cm., the relation employed in most clinical work. We finally used the average of all the calibrations to correct the measurements made on each curve, but the calibrations were very consistent in most experiments and it would have made little difference had the calibration which followed each systole been used for the ballistocardiogram preceding it.

Pulse wave velocities were measured by the distance between the first rise of the aortic and femoral pressure curves from their diastolic levels. This distance was referred to the time record; correction for alignment was rarely necessary. Duration of ejection was similarly measured from the syringe record.

The record of the syringe position, the cardiac output at each instant, was calibrated from the many readings of the syringe scale made before and after each systole.

Statistical analysis of the results was performed by standard methods. We are indebted to Dr. S. I. Askowitz for calculating the kinetic energy of the mallet blows used from the laws of the pendulum and for instruction in the use of a modern calculating machine for the statistical calculations.

On Various Technical Difficulties and Their Solutions

It was essential to the success of the experiment that the pistons move in their cylinders with a minimum of friction and without sticking, accordingly the syringes were taken apart and thoroughly washed at the end of each experiment, stored dry, and oiled with a mixture of light lubricating oil and "penetrating" oil when reassembled just prior to the first "systole" of the next experiment.

The use of water as perfusing fluid caused many difficulties. The aortic run-off was abnormally rapid and the perfusion bottle had to be elevated far above the theoretic diastolic level before "normal" diastolic pressures could be secured. Also because of the rapid run-off, if inflow from the perfusion bottle was interrupted, diastolic pressure fell off too fast before systole could be delivered. Therefore femoral inflow was continued during systole, a technic not ideal because the fluid entering the aortic "wind kessel" during systole consisted of both the "cardiac output" and a certain much smaller but unmeasured amount entering simultaneously via the femoral cannula. It was our belief that this systolic femoral flow compensated for the increased run-off of water during systole, as it surely did during diastole since it maintained that pressure constant.

Finally, in order to provide hypertensive pressures in the experiments in which water was used, elevation of the perfusion bottle to the ceiling was often not sufficient and the fluid had to be squirted into the femoral artery under pressures derived from the water mains. All these difficulties disappeared as soon as blood replaced water as perfusing fluid.

We struggled to reproduce the ballistic I wave at will during the first year of this investigation. The J and K waves occurred regularly after simulating systole, but in certain early cadavers the I wave failed to appear. We finally learned that three conditions must be met before an I wave can be secured; first, the cannulas must be of a size to contain a sufficient mass of blood moving headward; second, the cannula tips must be tied into the base of the aorta to provide an elastic tube which slows the transmission of the headward fluid wave and so separates the footward and headward forces which form the I and J waves; third, the cardiac ejection curve must rapidly accelerate early in systole to provide forces adequate to move the body footward before they are overcome by the larger headward components which follow so shortly after. By attention to these three needs, we reproduced ballistic "I" waves at will in 60 consecutive systoles and learned how to make them appear and disappear. So we now regard the problem as solved.

The plan of our experiments required satisfactory duplication of the conditions under which they were conducted. It was easy to hold constant the force of the blow and the amount of the padding, but to secure exactly similar resistance by attaining identical blood pressures proved more difficult. The diastolic perfusion bottle could readily be placed at the same height when duplicate pressures were desired, but the diastolic pressure attained at the instant before systole depended not only on the perfusing force but also on the length of

time the perfusion was allowed to run, a time which had to be judged for each experiment by watching the shift of the manometer beams. Also, after the inflow from the perfusion had been stopped, the time between the interruption of perfusion and the systolic blow played a large part in the height of the diastolic pressure. Thus our attempts to secure identical pressures in pairs of experiments were not always successful and we generally accepted as satisfactory only those experiments in which the diastolic pressures of the pair differed by less than 10 mm. Hg.

The Material

We aimed to perform our physiologic necropsy very soon after death and occasionally this was possible. Usually permission could not be secured until some hours had elapsed and about two hours more was required to assemble the team and set up the experiment. On one occasion, due to a misunderstanding of the day of death, we worked more than 24 hours after death had taken place. Experience slowly led to the realization that we could not distinguish clearly between results secured on fresh and old cadavers.

The complete pathologic reports on the 24 cadavers obviously cannot be given in detail and since the main emphasis of our work will be on the six in which blood was used as perfusing fluid, the pathologic picture of these subjects only will be presented.

No. 24. Feb. 12, 1952. P. L. Age: 47. Ht.: 167 cm. Wt.: 56 Kg. Blood pressure during life: 120/70 mm. Hg. Clinical diagnosis: carcinomatosis, jaundice, cholemic nephrosis. In the aorta numerous atheromatous plaques were present, but no ulceration nor calcification was found. The aortic diameter above the heart was 1.9 cm.

No. 25. Feb. 20, 1952. M. L. Age: 43. Ht.: 163 cm. Wt.: 70 Kg. Blood pressure during life: 118/60 mm. Hg. Clinical diagnosis: acute myelogenous leukemia. Pathologic diagnosis: acute myelogenous leukemia, with widespread local hemorrhages. A mild degree of atheromatous thickening was present in the aorta, particularly in the abdominal portions. There was no fibrosis, ulceration, or calcification seen. The pulmonary arteries were not remarkable. Lungs showed focal hemorrhages. The aortic diameter above the heart was 1.8 cm.

No. 26. March 5, 1952. H. Z. Age: 67. Ht.: 176.5 cm. Wt.: 74 Kg. Blood pressure during life: 116/80 mm. Hg. Clinical diagnosis: cardiac infarction. Pathologic diagnosis: generalized arteriosclerosis. Multiple old and recent infarcts of myocardium. Duodenal ulcer, benign prostatic hypertrophy. There was marked atherosclerosis with ulceration of the abdominal aorta, but in many places the arteries were in good condition. The aortic diameter above the heart was 2.5 cm.

No. 27. March 19, 1952. R. R. Age: 74. Ht.: 156 cm. Wt.: 49.5 Kg. Blood pressure during life: 140/80 mm. Hg. Clinical diagnosis: carcinoma of transverse colon, removed at operation. She was readmitted for closure of colostomy, but the lower bowel perforated and she died suddenly soon after. Pathologic diagnosis: generalized peritonitis, old and fresh myocardial infarcts, bronchopneumonia of lower lobe, bilaterally, petechial hemorrhage in pons. The aorta showed widespread marked atherosclerosis with large patches of calcification and many ulcerated areas. It was cut with scissors only with difficulty. The diameter of aorta above the heart was 3.7 cm.

No. 28. March 28, 1952. J. W. Age: 68. Ht.: 159 cm. Wt.: 43 Kg. Blood pressure during life: 112/68 mm. Hg. Clinical diagnosis: carcinomatosis following carcinoma of sigmoid, septicemia. Pathologic diagnosis: recurrent carcinoma of the colon with metastasis to regional lymph nodes, bronchopneumonia, acute pyelonephritis, ureteral obstruction. Aorta dilated and uncoiled, contains numerous atherosclerotic plaques and ulcerations. The section showed calcification of the media and intima of the aorta, with cholesterol clefts in the intima. At 4 cm. above the common iliac the aorta was narrowed to two-thirds its normal diameter by pressure from the tumor. The diameter of the aorta above the heart was 3.2 cm.

No. 29. May 20, 1952. M. McD. Age: 43. Ht.: 176 cm. Wt.: 98 Kg. Blood pressure during life: 135/85 mm. Hg. Clinical diagnosis: chronic myelogenous leukemia, terminal cerebral vascular accident. Pathologic diagnosis: chronic myelogenous leukemia, pulmonary edema with atelectasis of left lower lobe. The head was not examined. Aorta and arteries were normal, smooth and glistening. The aortic diameter above the heart was 2 cm.

Results

Design of the Experiments. The study was designed to determine the effects on blood pressure and ballistocardiogram of changes in these items: the energy of the systolic blow, the manner of application of that energy, the resistance to cardiac ejection as judged by the

diastolic pressure, and the amount of arteriosclerosis in the subject. We aimed to secure the advantages accruing to any statistical analysis when the experiments are paired. Accordingly the systoles were arranged in pairs which may be called A_1 and A_2; B_1 and B_2, etc. Usually both A_1 and A_2 were performed on the same subject and everything was kept as constant as possible except the single item being studied, which was larger in A_1 than in A_2 or vice versa. On the other hand, the range of the experience was kept wide by conducting the paired experiments under very different physiologic conditions; thus when changes in the force of the blow were being studied A_1 and A_2 were conducted at normal pressure; B_1 and B_2 with the same mallet padding but at hypertensive pressures; C_1 and C_2 at normal pressures with the mallet more heavily padded; E_1 and E_2 in an arteriosclerotic subject, etc. Thus while the range of the experience was great, the effect of the energy of the blow could be decided by studying the differences between results secured in each pair, A_1–A_2, B_1–B_2, etc. Obviously if changes in the energy of the blow were without effect, the mean of the differences of results secured in each pair, $\frac{(A_1–A_2) + (B_1–B_2) + \ldots (n_1–n_2),}{n}$ would approach zero, and if we can establish that this mean is significantly different from zero we have the right to believe that changes in the energy of the blow caused the differences in result we measure. Conventionally significance is established if t exceeds 2, which indicates a probability of about 95 in 100 that the result was not due to chance, and so t has been given under every item recorded in the tables.

In designing this series of experiments we were content to leave randomization of the data to chance; this was completely successful, for in the experiments with blood as perfusing fluid the larger of the values being studied came from an experiment performed first in 47 per cent of the pairs, from that performed second in 53 per cent.

Believing that to give all the raw data would overweight the paper with figures, we have presented in the tables the results of typical experiments chosen to illustrate the range of the experience, and the manner of taking the differences, as well as the statistics of each series as a whole.

Duplicate Estimations. The results of three typical pairs of duplicate estimations, all made with blood as perfusing fluid, and a statistical analysis of results secured on a total of 16 such pairs are given in table 2. By such duplicates we tested our ability not only to secure similar results in consecutive experiments, but also to return to the original conditions at the end of the experiment after many factors had been altered. It is evident that we were able to get reasonably satisfactory duplicates of the items measured. The systolic pressure varied most, as measurements sometimes made at the tip of a spike are likely to do. In the ballistocardiograms the I + J distance could be somewhat more closely duplicated than the J + K distance by blows judged to be similar.

These data provide a basis for judging the significance of changes in any of the functions measured when the experiment was altered. Accordingly three pairs of experiments were performed in which results secured with water as perfusing fluid could be compared with those obtained when blood was employed. The average difference between these pairs was not larger than the average difference between duplicate estimations (table 2) in which blood was employed in both experiments of each pair.

Also in six pairs of experiments we sought to answer the question whether clamping of the inflow from the perfusion bottle before the systolic blow (our final technic) yielded different results from those obtained when the inflow was allowed to continue during systole (our initial technic). We were unable to establish any significant difference in the resulting ballistocardiograms.

Effect of Increasing the Blow. Several typical experiments and the averages of the whole series of 15 pairs are given in table 3. An increase in the force of the blow never failed to increase the amplitude of the ballistocardiogram. The average increment of the force of the

blow was 12.7 × 10^6 ergs and this caused highly significant increases in systolic pressure, stroke volume, and in the amplitude of the ballistocardiogram.

The effect of changing the force of the blow on the ballistocardiogram is also illustrated when the I + J distance is plotted in relation to the kinetic energy of the blow (fig. 5). The effect of differences in mallet padding and in blood pressure is manifested by the dif-

TABLE 2.—*Duplicate Estimations. Force of the Blow, the Padding and the Diastolic Pressure are Held Constant, or Nearly so, in Each Pair. Data on Three Typical Paired Experiments and Statistics on the Differences between 16 Such Pairs*

Subject and Systole No.	Energy of Blow *ergs* × 10^{-6}	Padding Number	Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec.*	Ballisto	
			Dias. *mm. Hg*	Syst. *mm. Hg*				I + J *mm.*	J + K *mm.*
H. Z. 5	32.83	3	78	193	67	0.35	10.6	19.2	20.4
6	32.83	3	69	190	69	0.34	11.1	21.7	23.4
Difference			9	3	2	0.01	0.5	2.5	3.0
P. L. 5	5.21	2	69	86	24	0.46	5.0	3.6	5.4
6	5.21	2	60	75	18	0.32	4.1	2.6	3.5
Difference			9	11	6	0.14	0.9	1.0	1.9
J. W. 6	14.85	2	51	90	36	0.34	5.9	10.8	8.5
8	14.85	2	52	87	36	0.26	6.6	10.8	11.7
Difference			1	3	0	0.8	0.7	0	3.2
Statistics on the differences between 16 such pairs									
Differences without regard to sign									
Mean of differences.....			4.4	7.2	4.1	0.05	0.75	2.8	4.4
σ.....			3.1	5.1	2.9	0.04	0.62	2.3	2.5

TABLE 3.—*Effect of Increasing the Systolic Blow on the Ballistocardiogram. Data of Three Typical Paired Experiments and Statistics of 15 Similar Pairs in Which Padding and the Diastolic Pressure Were Held Constant, or Nearly so, in Each Pair*

Subject and Systole No.	Energy of Blow *ergs* × 10^{-6}	Padding Number	Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec.*	Ballisto	
			Dias. *mm. Hg*	Syst. *mm. Hg*				I + J *mm.*	J + K *mm.*
P. L. 11	14.85	2	123	192	38	0.24	9.2	4.6	8.4
10	32.83	2	119	232	56	0.28	9.2	6.9	15.4
Difference	+17.98	0	−4	+40	+18	+0.04	0	+2.9	+7.0
R. R. 11	11.71	3	79	116	23	0.30	7.0	5.3	5.8
10	32.83	3	78	174	50	0.24	7.0	20.0	25.8
Difference	+21.12	0	−1	+58	+27	−0.06	0	+14.7	+20.0
J. W. 12	14.85	2	48	80	48	0.36	6.8	8.3	5.8
14	19.24	2	43	96	51	0.35	5.6	12.5	11.7
Difference	+4.59	0	−5	+16	+3	−0.01	−1.2	+4.2	+5.9
Mean difference of 15 pairs.....	+12.70	0	−2.2	+22.5	+14.9	+0.008	+0.07	+6.8	+7.2
σ_m.....			1.23	6.08	3.07	1.45	0.55	1.53	2.46
t.....			1.78	3.70	4.87	0.55	0.01	4.4	2.92

ferences in I + J amplitude caused by similar blows. But when padding and resistance are the same—such points have been joined by lines in figure 5—one sees at once that for each situation the amplitude of the ballistocardiogram is proportional to the kinetic energy of the blow; indeed the relation is extraordinarily close, most of the lines pointing almost exactly at the origin.

Effect of Changing the Padding on the Mallet. This effect was investigated in eight pairs of experiments performed on three subjects. The systolic blow was the same and resistance was kept as similar as possible in both members of each pair while the padding was changed in one. The different pairs were performed under most dissimilar conditions; thus some pairs were made when the blow was strong, others when it was weak; some were made when the pressure was normal, others at shock levels; there were pairs in a subject with normal vessels, M. M., and pairs in one, R. R., who had marked arteriosclerosis and a dilated aorta. These diversities account for the great differences in results when the padding is similar.

The typical results and the statistics given in table 4 show clearly that an increase in

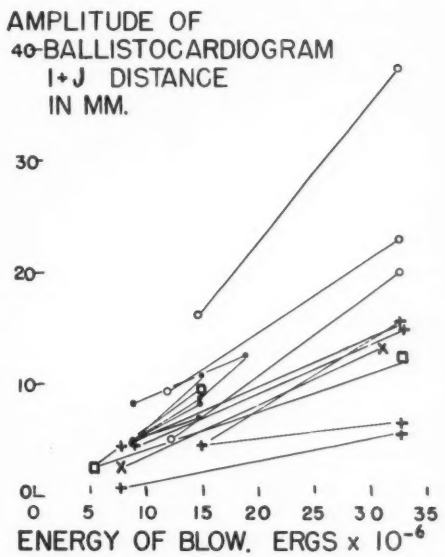

FIG. 5. Relation of the strength of the blow to the amplitude of the ballistocardiogram. Symbols: dots = subject J. W.; circles = R. R.; crosses = P. L.; squares = M. L.; x's = M. M. The symbols joined by lines indicate results secured in pairs of experiments on the same subject in which padding was constant, blood pressure was kept nearly constant, and the force of the blow varied. Blood was used as perfusing fluid in all cases except one pair of experiments performed on P. L.; in this pair water was used.

TABLE 4.—*Effect on the Ballistocardiogram of Softening the Systolic Blow by Increasing the Padding on the Mallet. Data of Three Typical Paired Experiments and Statistics of All Eight Pairs in Which the Force of the Blow and Diastolic Pressure Were Held Constant, or Nearly so, in Each Pair*

Subject and Systole No.	Energy of Blow *ergs* × 10^{-6}	Padding Number	Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec.*	Ballisto	
			Dias. *mm. Hg*	Syst. *mm. Hg*				I + J *mm.*	J + K *mm.*
M. McD. 6	19.24	1	66	83	51	0.32	5.0	16.1	20.2
5	19.24	4	61	77	68	0.64	4.6	2.0	3.2
Difference			−5	−6	+17	+0.32	−0.4	−14.1	−17.0
H. Z. 2	14.85	2	59	139	56	0.36	10.6	16.7	16.7
4	14.85	3	63	133	47	0.34	11.1	11.3	12.2
Difference			+4	−6	−9	−0.02	+0.5	−5.4	−4.5
R. R. 5	32.83	2	69	155	46	0.22	9.1	38.4	47.0
10	32.83	3	78	174	50	0.26	7.0	20.0	25.8
Difference			+9	+19	+4	+0.04	−1.9	−18.4	−21.2
Statistics: mean difference of 8 pairs	0		+6	+5.4	+3.6	+0.08	−0.26	−12.4	−15.4
σ_m			4.2	3.9	2.9	0.05	3.3	3.2	4.6
t			1.4	1.3	1.2	1.5	0.1	3.9	3.4

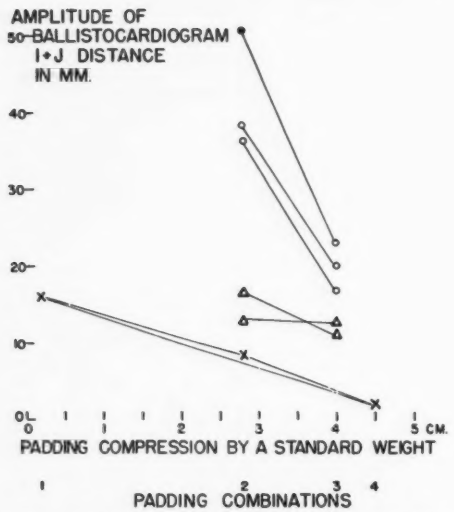

FIG. 6. Relation of the amount of padding cushioning the mallet's blow to the amplitude of the ballistocardiogram. Symbols: circles = subject R R.; x's = subject M. M.; triangles = subject H. Z. The symbols joined by lines indicate results secured in pairs of experiments on the same subject in which the force of the systolic blow and the diastolic pressure were kept constant or nearly so, the padding being varied. Blood was used as perfusion fluid in all these experiments.

The effect of increasing the padding on the amplitude of the ballistocardiogram is also shown in figure 6 where members of each pair are joined by lines. A change in the amount of padding on the mallet profoundly alters the response of the ballistocardiogram to blows of similar total energy, and the slopes of the lines indicate that the relation is roughly proportional, a similar change of padding affecting the larger values more than the smaller ones.

Effect of Changing the Resistance. This effect was sought by setting up pairs of experiments in single subjects in which the blow and padding were similar in each, but the diastolic pressures differed greatly, always by more than 10 mm Hg. Each of the five subjects perfused with blood was used and the 29 pairs were conducted under widely different conditions of blow, padding and pressure, the latter falling into several groups depending on the pressure levels. Thus in seven pairs we studied the effect of a change in diastolic pressure from a normal level (defined as from 85 to 65 mm. Hg) to the level found in mild shock (defined as from 65 to 40 mm. Hg), in seven pairs the effect of change from a normal level to that of severe shock (defined as under 40 mm. Hg), and in seven pairs the change from mild to severe shock. Table 5 gives the results of three such pairs of experiments which are typical of the others, and table 6 gives the results of

TABLE 5.—*Effect of Changing Blood Pressure. Data on Three Typical Paired Experiments Selected from 37 in which the Force of the Blow and Padding Were Held Constant in Each Pair*

Subject and Systole No.	Energy of Blow *ergs* $\times 10^{-6}$	Padding Number	Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec.*	Ballisto	
			Dias. *mm. Hg*	Syst. *mm. Hg*				I + J *mm.*	J + K *mm.*
R. R. 10	32.83	3	78	174	50	0.26	7.0	20.0	25.8
9	32.83	3	30	69	69	0.30	3.3	23.6	26.0
Difference			−48	−105	+19	+0.04	−4.6	+3.6	0.2
P. L. 5	32.83	2	120	236	58	0.26	8.3	7.6	16.6
6	32.83	2	78	160	61	0.30	4.6	5.8	15.6
Difference			−42	−76	+3	+0.04	−3.7	−1.8	−1.0
H. Z. 8	14.85	2	89	173	42	0.20	11.5	16.9	21.8
7	14.85	2	36	78	63	0.42	6.0	27.7	33.1
Difference			−53	−95	+21	+0.22	−5.5	+10.8	+11.3

padding causes a profound and significant diminution in the average amplitude of the ballistocardiogram for any given blow without causing significant changes in the averages of the other functions measured.

statistical analysis of all the data secured when blood was employed.

Unfortunately the results secured with blood as perfusion fluid contained only three pairs in which the effect of hypertensive blood pressures (defined as over 85 mm. Hg diastolic) could be studied, and in two of these the pressure was elevated very little above the upper normal limit. Therefore, we turned to the results of earlier experiments in which water had been used as perfusion fluid and found eight satisfactory pairs in which results obtained during hypertensions which ranged from 144/103 to 277/141 mm. Hg, could be compared with those found under similar conditions except for much lower pressures. The statistics of this series and of the entire series are also given in table 6.

TABLE 6.—*Statistics on the Effect of Alterations in Blood Pressure on the Ballistocardiogram. Statistics of the Differences between Paired Experiments Such as Those in Table 5, the Force of Systolic Blow and Padding Held Constant in Each Pair*

Type of change in B.P. studied and nature of perfusing fluid	Number of pairs	Statistics of differences between pairs					Ballisto	
		Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec.*	I + J *mm.*	J + K *mm.*
		Dias. *mm. Hg*	Syst. *mm. Hg*					
Blood. Normal diastolic pressure to mild shock.	7							
mean		−20.7	−18.3	+8	+0.06	−1.14	−0.47	+0.82
σ_m		2.46	4.3	2.35	0.016	0.48	1.25	2.16
t		11.9	4.2	2.9	3.4	2.4	0.4	0.4
Blood. Normal diastolic pressure to severe shock	9							
mean		−39.5	−66.4	+15.1	+0.09	−2.83	+3.9	+4.3
σ_m		3.08	7.0	1.45	0.02	0.66	1.96	2.64
t		13.0	9.5	9.15	4.4	4.7	2.0	1.63
Blood. Mild shock to severe shock	8							
mean		−19.1	−30.6	+8.9	0.05	−1.02	−0.1	−2.0
σ_m		3.5	3.0	2.4	0.01	0.2	1.16	1.51
t		5.4	10.0	3.7	4.0	5.1	0.1	1.4
Water. Hypertension to normal pressure or below	8							
mean		−63.0	−77.0	+11.4	+0.07	−3.66	+7.9	+8.5
σ_m		10.2	18.5	1.3	0.01	0.73	3.2	3.5
t		6.2	4.1	8.8	6.1	5.0	2.5	2.4
All the data, the experiments used above plus 5 other experiments	37							
mean		−35.2	−49.3	+10.8	+0.07	−2.42*	+2.6	+1.8
σ_m		3.7	5.6	0.98	0.02	0.36	0.99	1.33
t		9.6	8.8	11.0	3.5	6.8	2.6	1.4

* Pulse wave velocity estimated in 30 pairs only.

The results show that many physiologic measurements changed profoundly when blood pressure was altered in our experiments. Thus when blood pressure was lowered, the stroke volume delivered by the same systolic blow regularly increased because resistance to the

inflow of fluid into the aorta had been lessened; the duration of ejection also increased, and the pulse wave velocity was markedly diminished. In contrast to these major changes, the effect on the ballistocardiogram amplitude was small, but in the series as a whole the average change does attain significance, and this is also true in those smaller groups in which the average change in blood pressure was very great. Nevertheless, in comparison with the major changes of blood pressure, pulse wave velocity and duration of ejection found in these experiments, the effect on the ballistocardiogram seems almost negligible.

TABLE 7.—*The Effect of Arteriosclerosis. Data on Three Typical Paired Experiments and Statistics on 12 Such Pairs in which the Blow and Padding Were Constant and the Blood Pressures Matched as Closely as the Data Permitted; One Subject of Each Pair Being Arteriosclerotic While the Other Was Not*

Subject and Systole No.	Arterio-sclerosis	Energy of Blow *ergs* $\times 10^{-6}$	Padding No.	Femoral B.P.		Stroke Volume *cc.*	Duration of eject. *sec.*	Pulse wave velocity *M. per sec*	Ballisto	
				Dias. *mm. Hg*	Syst. *mm. Hg*				I + J *mm.*	J + K *mm.*
R. R. 2	+++	14.8	2	58	109	35	0.28	5.7	18.6	23.5
M. L. 1	0	14.8	2	55	104	61	0.45	5.1	8.0	10.4
Difference				+3	+5	−26	−0.17	+0.6	+10.6	+13.1
R. R. 5	+++	32.8	2	69	155	46	0.22	9.1	38.4	47.0
M. L. 3	0	32.8	2	57	118	63	0.28	4.6	12.5	16.7
Difference				+12	+37	−17	−0.06	+4.5	+25.9	+30.3
J. W. 14	++	19.2	2	43	96	51	0.35	5.6	12.5	11.7
M. M. 4	0	19.2	2	51	80	58	0.36	4.8	8.9	15.4
Difference				−8	+16	−7	−0.01	+0.8	+3.6	−3.7
Statistics on the differences between 12 such pairs										
Mean difference				−3	+3	−12	−0.07	+2.18	+9.8	+8.7
σ_m				4.53	8.38	3.80	0.02	0.56	3.31	4.54
t				0.79	0.36	3.07	3.72	3.89	2.97	1.91

Effect of Arteriosclerosis. The data permitting this study were assembled with more difficulty because the results paired came from experiments on different subjects, and so were secured on different days, often months apart. The lack of certain knowledge whether the subject had arteriosclerosis or not, a fact determined at the necropsy conducted after our experiments were over, added to the difficulties of following any prearranged plan.

Of our subjects perfused with blood, one, M. M., was without arterial lesions; in two, M. L. and P. L., there were only some superficial yellowish patches; while in H. Z. and J. W. arteriosclerotic changes were marked, and in R. R. they were most advanced; so it seemed proper to assess the effect of this abnormality by comparing results secured in the first three with those obtained in the last three, and many such pairs could be made up from our data.

For the reasons given agreement within the pairs was not always as close as that we had demanded in the pairs studied hitherto. For example, among the 12 pairs statistically studied with the results given in table 7, in only seven was the agreement of diastolic pressures within 10 mm.; we accepted the less perfect five because in the series as a whole the average difference of diastolic pressure within the pairs was close to zero, and because data in the preceding section showed clearly that differences in diastolic pressures had little effect on the ballistocardiogram. But we have also studied three other pairs, in which results secured in our most arteriosclerotic subject could be paired with those obtained in subjects with less arteriosclerosis, and these results are perfectly consistent with the statistics given in table 7. So our data indicate that in the pres-

ence of severe arteriosclerosis a given systolic blow was followed by a significantly smaller stroke volume and a shorter duration of ejection, while pulse wave velocity was increased, and pulse pressure was not significantly changed. In addition, the amplitude of the ballistocardiogram, judged by the average I + J distance was increased significantly, but the increase in the average J + K distance was not significant.

Discussion

The question whether results secured soon after death could be properly applied to the living has been always before us and our efforts to discover differences between the physical properties of our cadaver preparations and those of living persons have continued unabated. The present status of our knowledge of this subject will now be reviewed.

The vibration period of our subjects, estimated from the vibrations following a single tap is always within the range of similar data secured on the living.

The damping of our 24 cadavers on the ballistic table, estimated by the response to lifting off the calibrating weight, is almost exactly critical, or somewhat less than critical. It is harder to estimate the degree of damping in living persons, but the rough tests possible suggest that the situation is much similar in these.

The contours of the femoral blood pressure curves of our preparations seem identical with those secured in living subjects except that in many of our records the dicrotic notch is less prominent. We attribute this to the absence of functioning aortic valves in our preparation, in which the reflected pulse wave must overcome the resistance in the syringe before the piston is forced back against the next tooth of the ratchet. This does often take place and a notch appears on the blood pressure curve at this instant.

The pulse wave velocities in our subjects vary widely with their age, with the degree of arteriosclerosis, and with the diastolic pressure employed. The pulse wave velocities of living persons vary similarly, and we see no noteworthy difference between our results and those to be expected from experience in the clinic. Thus, as far as the systemic circulation is concerned, we have sought diligently for differences between the results secured in our cadavers and those expected in living subjects and have found very few.

Studies of the pulmonary side of our subjects have disclosed more differences from the normal. The pulmonary diastolic pressure, measured before each systole, was set at a normal level, but the peak of the pulmonary systolic pressure, measured in five systoles in two cadavers, was always higher than corresponding measurements in healthy persons would have led one to expect. Thus in two systoles of experiment 29 with pulmonary diastolic pressures of 0 and 3 mm. Hg the pulmonary systolic pressures measured from the top of the spike were 39 mm. Hg in both. Obviously, there was more resistance in the lungs of our subjects than normal, doubtless because the lungs were collapsed, and possibly also because terminal pneumonia and pulmonary edema were found frequently in our preparations.

Finally, the ballistocardiograms in our experiments are identical with those found in living subjects as far as the main systolic waves are concerned. But there is no "H" wave in any of these records, and in early diastole the pattern of small L waves followed by larger N waves, often but not always seen in healthy persons, occurs very rarely.

By means of Bazett's formula[5] a "pulse rate per minute" can be estimated for each systole in our experiments, from the measured duration of ejection and by making an allowance of one-sixth the duration of systole for the preejection phase of cardiac contraction. The value obtained can be applied to the stroke volume measured to give a "cardiac output per minute" for each of our "systoles," and by using the subject's surface area a "cardiac index" as well. The range of these results in our experiments is given in table 8, in which the range of our other measurements is also shown. This table shows clearly that we have worked within the range of values found in the clinic. The great diversity of physiologic conditions found in our experiments was delib-

erately sought. The lowest of our "shock" experiments might be criticized as being conducted at levels seen only in moribund patients, but to us they do not lose interest on that account.

The experiments described have identified two factors of primary importance in the genesis of the ballistocardiogram, the energy of systole and the manner in which that energy is applied. Both deserve discussion and the first is subject to certain qualifications.

By the physical laws of the pendulum one can calculate the energy delivered by the mallet which, by driving in our syringe pistons, simulated systole; we have used the results of such calculations as the basis of comparison with ballistocardiogram amplitudes in figure 3. But a large portion of the energy applied is lost by friction in the syringes; the expectation from other piston systems is that over 80 per cent will be so lost. By analysis of our curves we have the data to calculate the energy delivered directly into the aorta but to discuss this now is to exceed the scope of this paper; we plan to present data based on dynamic analysis of the curves in later communications. Here we are content to assume that the energy transmitted to the great vessels will vary directly with the force of the blow; indeed, experiments cited in figure 3 satisfy us that this is the case.

TABLE 8.—*Ranges of Physiologic Measurements in these Experiments*

	Highest	Lowest
Age of subjects (*years*)	74	43
Weight of subjects (*Kg.*)	98	43
Systolic blood pressure (*mm. Hg*)	277	45
Diastolic blood pressure (*mm. Hg*)	141	19
Pulse wave velocity (*M./sec.*)	12.9	3.9
Duration of ejection (*sec.*)	0.64	0.19
Pulse rate (estimated) (*per min.*)	200	30
Stroke volume (*cc.*)	69	22
Cardiac output (estimated) (*L./min.*)	6.4	0.78
Cardiac index (estimated) (*L./min./M.²*)	4.4	0.4

Experiments in which the force of the systolic blow was varied were made in each of the six cadavers perfused with blood and in each of the 18 perfused with water in this series; these experiments were usually made more than once in each cadaver. When other conditions were kept constant we encountered no instance in which a larger systolic blow was not followed by an increased amplitude of the ballistocardiogram as judged by the I + J distance. This was almost always true of the J + K distance also, but this measurement behaved with a little more variability than the I + J distance, as the statistics given in the tables show. Obviously therefore, the kinetic energy imparted to the blood by the heart's contraction is a major factor in the amplitude of the ballistocardiogram.

But the results of the experiments on changing the padding on the mallet indicate that there is a second factor of major importance. Again the results of our experiments were completely consistent. Neither in the cadavers perfused with blood, nor in those perfused with water have we ever encountered an experiment in which, the blow and pressure remaining constant, an increase in the padding on the mallet was not followed by a decreased amplitude of the ballistocardiogram; often this decrease was profound. Obviously, therefore, in addition to the energy of the cardiac blow we have demonstrated a second factor of major importance in the interpretation of ballistocardiogram amplitude.

The nature of this effect can be readily realized by readers without mathematical background by drawing an analogy to driving a nail with a hammer. As the iron of the hammer strikes that of the nail the energy of the former is delivered to the latter almost instantaneously, and the nail is driven in. But if one places a rubber pad over the head of the hammer and strikes the same blow, the nail is moved little if at all; for the energy of the hammer blow, although its total is the same as when no pad was present, is no longer delivered instantaneously but spread out in time. Thus to drive a nail one needs energy delivered in concentrated form; one needs a high energy per unit of time. The ballistocardiogram evidently depends on the energy per unit of time delivered by the heart,

and energy per unit of time is properly defined as a form of power. So it is proper to think of the amplitude of the ballistocardiogram as measuring the heart's power.

The question then arises, are there factors in the body which might disturb the usual relationship between cardiac power and ballistic amplitude and so interfere with the proper estimation of the heart's power from that record? We have investigated two such factors, the height of the blood pressure and the presence of arteriosclerosis.

The results indicate that the effect of changes in blood pressure on the amplitude of the ballistocardiogram for a given systolic blow is so small that it appears almost negligible. The statistics cited in table 6 show clearly that it takes a change of blood pressure of a magnitude seldom seen in the clinic, and a large number of experiments, to establish that there is any significant effect at all. When blood pressure is altered in our experiments, large and highly significant effects on cardiac output, duration of ejection and pulse wave velocity are demonstrated readily; in contrast the amplitude of the ballistocardiogram changes very little. But with enough experiments a significant correlation can be demonstrated and the slope of the regression given in table 9 could be used to correct the relation of the ballistocardiogram to cardiac power in patients studied under conditions in which diastolic blood pressure varies greatly, if such a small correction seemed worthwhile. Thus, if in any experiment the diastolic blood pressure increased 30 per cent, an 11 per cent diminution in the I + J distance should be attributed to this and not to a coincidental change in cardiac power.

The reason why differences in blood pressure alter the relation of ballistic amplitude to cardiac power was sought by the technic of partial correlation and the results are given in table 9. The changes of blood pressure in our experiments are strongly correlated with changes in pulse wave velocity, as was to be expected from old physiologic conceptions.[7] That an increase in pulse wave velocity could be expected to diminish the amplitude of the ballistic response to a given cardiac output was realized early,[9] the higher the pulse wave velocity the more overlapping of the forces delivered in opposite directions and the smaller the resultant which escapes to move the body. But it was also stated[9] that this effect was judged to be small, and this view now has experimental confirmation.

If this relation between pulse wave velocity and ballistic amplitude is neutralized by mathematical means, differences in blood pressure are no longer correlated with the amplitude of the ballistocardiogram and so it may be concluded that blood pressure changes affect the ballistocardiogram by altering pulse wave velocity.

In our study of the effects of arteriosclerosis we were forced to use different subjects in each pair, so there were factors other than the presence and absence of this abnormality which differed within the pairs, and such factors might play a part in the result secured. Thus our three arteriosclerotic subjects were

TABLE 9.—*Correlation Coefficients and Regression Equations*

Number	Relation	Correlation Coefficient	Level of Significance $p = 0.05$
1	Change in pulse wave velocity (%) and change in I + J distance (%)	−0.77	0.36
2	Change in diastolic pressure (%) and change in pulse wave velocity (%)	0.81	0.36
3	Change in diastolic pressure (%) and change in I + J distance (%)	−0.63	0.36
	Partial Correlation Change in diastolic pressure (%) and change in I + J distance (%) independent of pulse wave velocity		
	$r_{2.3.1}$ =	−0.02	
	($\sigma_{2.3.1}$ =	0.195)	

Regression Equation

Change in I+J (in %) = −0.36 [change in diastolic pressure (in %)]

Standard deviation about the regression (σ_{yx}) = 3.9%

much older than the three controls; they died of different causes and on the average, weighed less. Doubtless other differences between the two groups could be found, and results secured from such a series of pairs do not quite have the finality of those secured when experiments made on the same subjects are paired. Also in a forthcoming publication we will submit data demonstrating that body size of itself has an effect on the ballistocardiogram, and, our arteriosclerotic subjects being smaller, part of the difference between the ballistocardiograms of the two groups is due to this. But after correction for the difference in size, the arteriosclerotic subjects still have significantly larger I + J amplitudes, t being 2.65, so our finding is not explained by the difference in size of the subjects. Therefore, it seems proper to ascribe the differences found in our experiments to the arteriosclerosis which was present; indeed, our results confirm much that has been long known about this condition, as well as adding much that was new to us. The increased pulse wave velocity demonstrated in our arteriosclerotic subjects has long been known,[7] as has the increased peripheral resistance which can be estimated from our data. We were surprised that, after the systole of standard energy, arteriosclerosis caused a diminution in stroke volume rather than a significant increase in pulse pressure; one cannot diagnose arteriosclerosis from the pulse pressure alone in our experiments.

In contrast to these highly significant effects the influence of arteriosclerosis on the amplitude of the ballistocardiogram is less striking; only in the case of the I + J distance does it attain significance. However, we note that it is the striking differences secured in our oldest and most arteriosclerotic subject which make the data significant; if the four results on subject R.R. are omitted, the average I + J difference is more than halved and t falls to 0.87; so our results suggest that only in advanced cases would a significant effect be expected.

The reason for this larger ballistocardiogram in arteriosclerotic subjects deserves discussion. The increased pulse wave velocity is not responsible; this causes changes in the opposite direction. The increased mass of blood in the dilated aorta may well be a factor, but for theoretic reasons[8] we are inclined to weight another explanation more heavily. Stiffness of the aortic wall would alter the normal distribution of cardiac energy between potential and kinetic forms in favor of the latter, and it is kinetic energy which is the genesis of the ballistocardiogram. This view is supported by results secured on cadaver E.I. who died at the age of 50 of advanced scleroderma involving both skin and internal organs, and who was perfused with water early in our experiments. In this case the aorta was not dilated and it appeared normal to gross inspection, but after a standard blow an abnormally large ballistocardiogram resulted, an effect similar to that found in our most arteriosclerotic subject.

In any case the effect of peripheral arteriosclerosis, per se, is not responsible for the marked diminution in amplitude of the ballistocardiogram found in healthy persons as age advances[10]; its influence is in the opposite direction. The effect of the increase of blood pressure with age is too small to account for the diminution found in this amplitude[10]; therefore, this diminution has rightly been attributed to a decrease of cardiac power as age advances.[10]

Summary

During the last three years our technic for the simulation of systole in cadavers at necropsy has been much improved. At present, blood instead of water is used as perfusing fluid; systoles are powered by a known energy; blood pressure is measured simultaneously in both central and peripheral vessels. Since the last report[1] we have performed 305 simulated systoles in 24 cadavers, blood being used as perfusing fluid in 65.

By the method of paired experiments we have investigated the effect of changes in "cardiac function" on the amplitude of the ballistocardiogram and also the effect of peripheral factors which might of themselves influence the ballistic amplitude.

Increase in the energy of the "cardiac" blow regularly increased the amplitude of the resulting ballistocardiogram, other factors being held constant.

Softening the "systolic" blow by increased adding on the mallet markedly diminished the amplitude of the resulting ballistocardiogram even though the total energy of the blow remained the same. The ballistic amplitude is therefore determined by energy delivered per unit of time, thus by a form of power.

Large changes in blood pressure had only a small effect on the ballistic amplitude following a given blow, an effect to be attributed to the change in pulse wave velocity resulting.

Marked arteriosclerosis appeared to cause a significant effect, the ballistic amplitude being consistently larger than expected for a given blow in our oldest and most arteriosclerotic subject. When all the results were averaged I+J was significantly larger in the older and more arteriosclerotic subjects, but J+K was not.

In each subject as blood pressure was increased the pulse wave velocity also increased. Under comparable conditions the older and more arteriosclerotic subjects had faster pulse wave velocities than did the younger group who were either without vascular lesions, or had only minor changes. These observations confirm the currently accepted ideas about pulse wave velocity.

In our older and more arteriosclerotic subjects a standard systole caused a significantly smaller stroke volume than in our younger subjects, and the expected increase of pulse pressure in the arteriosclerotic subjects did not appear.

Acknowledgment

We are indebted to 10 members of the William Pepper Medical Laboratory and the Laboratory of Surgical Pathology who, under the direction of Dr. R. F. Norris and Dr. R. C. Horn, performed the necropsies on our 24 subjects; and we wish to thank them for bearing so patiently the irritations and delays that our experiments must have caused them.

Sumario Español

Este artículo describe los resultados obtenidos durante los últimos tres años con mayor énfasis en aquellos obtenidos desde el desarrollo de la técnica que permite el uso de sangre compatible como flúido de perfusión. Usando el método de experimentos pareados, datos se han obtenido de los efectos en la onda del pulso y el balistocardiograma, consiguientes a cambios en la energía total de un sístole simulado, cambios en la manera que la energía se aplica durante el sístole, cambios en resistencia determinados mediante la presión diastólica, y la diferencia en el grado de arterioesclerosis presente en varios sujetos.

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Observations on the Hemodynamic Properties of a Thiophanium Derivative, Ro 2-2222 (Arfonad), in Human Subjects

By N. S. Assali, M.D., Roy A. Douglass, Jr., M.D., and Roy Suyemoto

Observations on the hemodynamic properties of a thiophanium derivative (Arfonad) have been made on normotensive nonpregnant and pregnant subjects and on patients with hypertensive complications of pregnancy. The drug was given by single intravenous injections and by intravenous drip infusion. The hypotensive effects of single injections were compared with those of a standard tetraethylammonium chloride (TEAC) test. The authors observed that the hemodynamic effects of Arfonad were similar in some respects to those of tetraethylammonium chloride or spinal anesthesia. A fall in the cardiac output occurred when the blood pressure fell following Arfonad administration. The authors discuss these hemodynamic effects in terms of differences in response to ganglionic blocking agents of the various groups of subjects studied.

ANIMAL EXPERIMENTS carried out by Randall and his associates[1] have shown that the pharmacologic activities of certain thiophanium derivatives are similar in many respects to those of tetraethylammonium ion. The vasodepressor action of one of these compounds, d-3,4 (1′,3′-dibenzyl-2′-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate, known by its code number as Ro 2-2222 or commercially as Arfonad,* was found to be 30 times more potent than tetraethylammonium. Sarnoff and his associates[2] administered Arfonad to animals as well as to normotensive and hypertensive men and obtained a graded vasodepressor effect which was similar but preferable to spinal anesthesia. These authors also observed a blockade of the pressor response to cold and a rise in the skin temperature of the lower extremities. They concluded that the action of this drug is similar in some respect to that of ganglionic blocking agents. Green[3] gave the drug to normotensive subjects and also observed a marked rise in the skin temperature of the lower extremities, without much change in that of the upper extremities. McCubbin and Page,[4] on the other hand, believe that Arfonad in dogs acts directly on the vessel walls, the ganglionic blocking effects playing a minor role.

The present study was undertaken in order to investigate some of the hemodynamic effects of Arfonad in pregnant subjects. In previous studies[5, 6] we have shown that normotensive pregnant subjects respond with a marked fall in blood pressure to autonomic blocking agents in contrast to patients with toxemia of pregnancy in whom the response is negligible. It was thought that these contrasting results observed in these two groups of patients together with determination of responses to Arfonad in similar groups of subjects might throw light on the hemodynamic activities of Arfonad.

Material and Methods

The material consisted of 56 subjects comprising the following groups: (a) 10 normotensive nonpregnant subjects, (b) 20 normotensive pregnant subjects in the last trimester of gestation, (c) 10 patients with acute toxemia of pregnancy, and (d) 16 patients with essential hypertension associated with pregnancy.

The diagnosis of acute toxemia and of essential hypertension was made according to the criteria

From the Obstetric Research Laboratory and the Department of Obstetrics, University of Cincinnati College of Medicine and the Cincinnati General Hospital, Cincinnati, Ohio.

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* Arfonad was supplied by Hoffmann-La Roche, Inc.

outlined elsewhere.[6] All the patients were studied after they had been at bed rest in the hospital for approximately 24 hours. Arfonad was given by single intravenous injections in dosages varying from 0.03 to 0.2 mg per kilogram of body weight or by intravenous infusion in a solution of 5 per cent glucose and water containing 2 mg. of Arfonad per cubic centimeter. Single injections of different doses and intravenous infusion of the drug were frequently given to the same patient. The response to the effective single dose was compared with that to 400 mg. of tetraethylammonium chloride (TEAC) in the same subject.

Control blood pressure readings (sphygmomanometer) were taken in the supine position every one to two minutes for about 10 minutes prior to injection of the drug. Thereafter, readings were taken every half or one minute until the blood pressure had returned to preinjection levels. The mean arterial pressure was computed by adding one-third of the pulse pressure to the diastolic pressure.[7] Pulse rate was counted from the radial or carotid artery. Skin temperature was recorded by means of a Rauh pyrometer in a room kept at constant temperature. Cardiac output was measured by a high frequency ballistocardiograph.[8] It has been shown that this method is sufficient to give relative values for cardiac output before and after the administration of the drug. The one-minute cold pressor tests and the Valsalva maneuvers were performed once before and two to three times after the administration of the drug. Detailed studies of renal function were made on some of these patients and will be reported in a subsequent paper.[9]

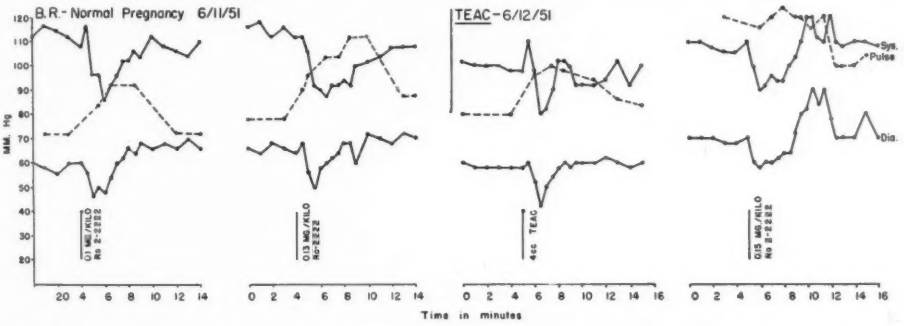

FIG. 1. Effects of single doses of Ro 2-2222 on the blood pressure and pulse rate in normal pregnancy as compared with a standard test with 400 mg. of tetraethylammonium chloride (TEAC). Note that there was insignificant difference between the effects of 0.1, 0.13, 0.15 mg. per kilogram and the TEAC test.

RESULTS

1. *Effects of Single Intravenous Injections*

Three normotensive pregnant subjects were given single injections of 0.03 mg. per kilogram; three others were given 0.05 mg. per kilogram; two received 0.07 mg. per kilogram and two received 0.09 mg. per kilogram. None of these patients showed any significant vasodepressor effect. Moderate tachycardia was present in the patients who received 0.07 and 0.09 mg. per kilogram.

The remaining normotensive pregnant and essential hypertensive pregnant patients received intravenous injections of Arfonad in doses varying from 0.1 to 0.2 mg. per kilogram. In this dosage, the drug evoked a significant fall in blood pressure which paralleled that produced by the injection of 400 mg. of tetraethylammonium chloride (fig. 1). The vasodepressor action of the single dose lasted for 3 to 10 minutes although in two normotensive pregnant subjects who received 0.15 mg. per kilogram the blood pressure remained low for approximately 30 minutes. At the height of hypotension, the pulse rate increased by an average of 30 beats per minute.

The toxemic and normotensive nonpregnant subjects were similarly given single doses of 0.1 to 0.2 mg. per kilogram. The fall in blood pressure in these two groups was less significant than in the previous groups. The pulse rate increased slightly in some cases and remained unchanged in others. No significant side effects such as dryness of the mouth and blurring of the vision were observed in any of the patients who received Arfonad in single injections.

2. Effects of Intravenous Infusion

This method of administration was used in 10 normotensive pregnant, 5 normotensive nonpregnant, 10 toxemic, and 12 essential hypertensive pregnant subjects. Arfonad was given in a solution containing 2 mg. per cubic centimeter, and the rate of infusion was regulated as to secure a significant fall in blood pressure. The response to the drug in these patients was taken as the average of the three lowest blood pressure readings observed during the infusion.

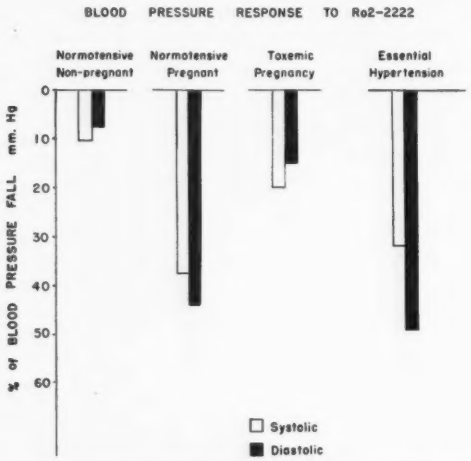

FIG. 2. Mean blood pressure response of the patients studied with intravenous infusion of Ro 2-2222. The maximum response was calculated from the average of the three lowest blood pressure readings during the infusion and plotted as per cent of the average control blood pressure. Note the marked fall in the blood pressure of normotensive pregnant and essential hypertensive pregnant subjects in contrast to the smaller fall in the blood pressure of toxemic and normotensive nonpregnant groups, despite the fact that the average rate of infusion in the last two groups was much higher (see text).

A. Blood Pressure and Pulse Rate. Normal pregnant and essential hypertensive pregnant subjects responded in the same manner to infusion of Arfonad. In the normotensive group, there was an average fall of 37 per cent in the systolic and 46 per cent in the diastolic blood pressure, the rate of infusion varying from 3 to 8 mg. per minute; in the hypertensive group, the fall averaged 32 per cent systolic and 49 per cent diastolic blood pressure, the rate of infusion varying from 6 to 18 mg. per minute (fig. 2). In all but three normotensive pregnant subjects, the vasodepressor action could be maintained for as long as the infusion was continued. In these three instances the vasodepressor action persisted for half an hour after the interruption of the infusion and then began to recede gradually. The majority of patients showed insignificant changes in pulse rate during the infusion. In four normotensive subjects the pulse rate increased about 20 beats per minute but returned to control levels while the blood pressure was still low.

Three normotensive pregnant subjects were given intravenous injections of 25 mg. ephedrine during Arfonad infusion. In each instance the blood pressure returned immediately to or became higher than the control levels (fig. 3).

Intravenous infusion of the drug to normotensive nonpregnant subjects in doses varying from 8 to 60 mg. per minute resulted in a fall in blood pressure to approximately 10 per cent of the control level (fig. 2). Tachycardia was present in two cases, but in the others the pulse rate did not change.

In the toxemic group, the intravenous infusion of Arfonad in doses varying from 8 to 30 mg. per minute produced an average fall of 22 per cent in systolic and of 17 per cent in diastolic blood pressure (fig. 2). Again, the pulse rate remained unchanged in the majority of cases.

B. Cardiac Output and Peripheral Resistance. Estimations of cardiac output and peripheral resistance were carried out on five normotensive pregnant, three essential hypertensive pregnant, and two normotensive nonpregnant subjects (table 1). Two to three determinations were made during the control period and 7 to 12 determinations during and after the infusion.

The normotensive pregnant and essential hypertensive pregnant patients who showed a significant fall in the blood pressure, also showed a decrease in the cardiac output varying from 0.5 to 2.2 liters per minute (table 1). The fall in the cardiac output was closely related to the fall in blood pressure and was mainly due to a decrease in the stroke volume (fig. 4). When the blood pressure did not change

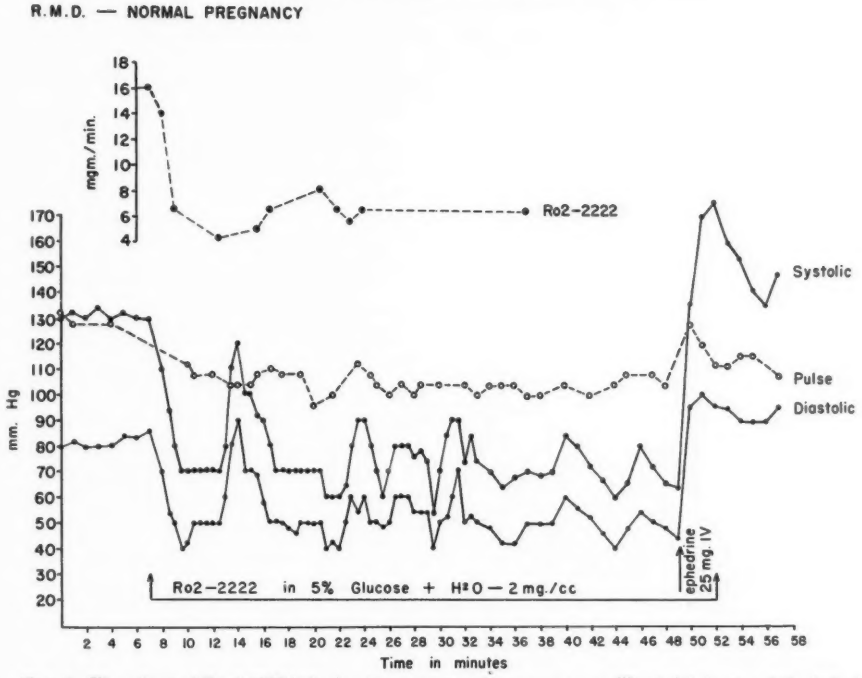

FIG. 3. The effect of Ro 2-2222 infusion in normotensive pregnancy. The initial rate of the infusion was 16 mg. per minute. This produced a severe drop in blood pressure with signs of circulatory collapse. These were improved and the blood pressure was kept around 90/50 by frequently readjusting the rate of infusion. The variations in blood pressure readings were probably due to variations in the rate of infusion. Note that the pulse rate showed insignificant changes. At 48 minutes, 25 mg. ephedrine were given intravenously. This produced a marked rise in the blood pressure.

TABLE 1.—*Cardiac Output and Total Peripheral Resistance Before and After Arfonad in Two Normal Nonpregnant Women, Five Normal Pregnant Women and Three Hypertensive Pregnant Women*

Patient	Diagnosis	Control				After Arfonad			
		Mean Arterial Pressure	Pulse	Cardiac Output	Total Periph. Resist.	Mean Arterial Pressure	Pulse	Cardiac Output	Total Periph. Resist.
A. N.	Normal pregnant	88	82	5.2	16.9	63	92	4.4	14.3
L. S.	Normal pregnant	93	92	5.8	16.0	54	96	5.3	10.2
N. J. R.	Normal pregnant	86	84	4.8	17.9	56	88	4.0	14.0
M. K.	Normal pregnant	95	88	6.1	15.6	53	92	5.0	10.6
F. B. L.	Normal pregnant	83	115	7.4	11.2	48	110	5.2	9.2
Average		89	92	5.9	15.1	55	96	4.8	11.7
J. T.	Essential Hypert. (preg.)	140	96	6.2	22.6	93	102	5.3	17.5
E. R.	Essential Hypert. (preg.)	130	102	6.8	19.1	89	110	5.3	16.8
E. F.	Essential Hypert. (preg.)	143	84	5.6	25.5	95	96	4.7	20.2
Average		138	94	6.2	22.4	92	103	5.1	18.2
T. W.	Normal nonpregnant	86	88	5.2	16.5	85	104	5.8	14.7
L. B.	Normal nonpregnant	91	90	5.8	15.7	85	96	5.7	14.9
Average		89	89	5.5	16.1	85	100	5.8	14.8

significantly, the cardiac output remained relatively unchanged.

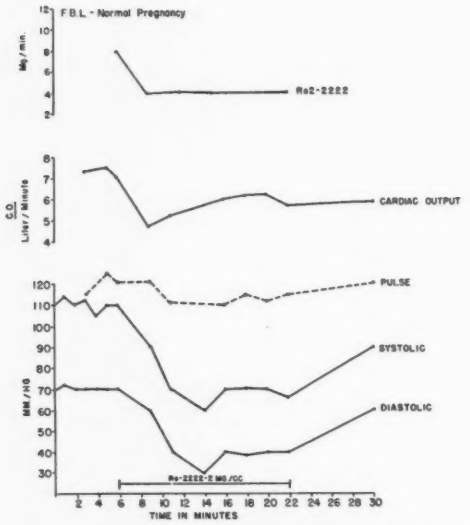

FIG. 4. Cardiac output determinations during Ro 2-2222 infusion. In this patient the cardiac output was reduced by about 2 liters at the height of blood pressure fall. Note the close relationship between blood pressure and cardiac output changes.

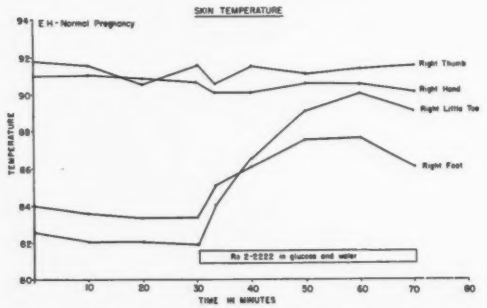

FIG. 5. Skin temperature changes during Ro 2-2222 infusion. This patient had a marked fall in blood pressure during the infusion. Note the marked rise in the temperature of the lower extremities and the negligible changes in that of the upper extremities. Similar changes were observed in all the subjects studied. The changes in the skin temperature did not show any relationship to the blood pressure response.

Total peripheral resistance was calculated from the formula: $R = \frac{Pm,}{CO}$ where R represents total peripheral resistance, Pm average estimations of mean arterial pressure and CO average values for cardiac output. The values for total peripheral resistance in the normal nonpregnant and normal pregnant subjects were approximately the same but they were slightly higher than normal values reported by Goldring and Chassis.[10] The values for the essential hypertensive pregnant group were similar to those reported by these authors. Arfonad produced an average fall of 24.8 per cent in the peripheral resistance of the normotensive pregnant group and 18.8 per cent in the essential hypertensive group. In the normotensive nonpregnant subjects the change was slight.

C. Skin Temperature. Three normotensive pregnant, two toxemic and two normotensive nonpregnant subjects were studied. The patients were maintained recumbent in a constant temperature room with the larger portion of the body uncovered for at least half an hour. Readings were then taken from different areas but additional attention was given to changes in the temperature of the extremities. In all patients, infusion of Arfonad was followed by a rise of 4 to 8 degrees in the skin temperature of the lower extremities, the temperature of the upper extremities remaining practically unchanged (fig. 5). The changes in skin temperature showed no relationship to the magnitude of blood pressure fall.

D. Vasopressor Reflexes. Five normotensive pregnant, two normotensive nonpregnant and four essential hypertensive pregnant patients were subjected to cold pressor tests by immersing the hand to the wrist in ice water for one minute. Some of these patients were studied with both single injections and intravenous infusion of Arfonad. All patients showed in the control period, a pressor reaction to cold of varying magnitude. After the administration of the drug the pressor reaction was partially or totally abolished (fig. 6).

The pressor response to the Valsalva maneuver was also studied in some of these patients. In all but one case, there was a partial or total blockade of the Valsalva "overshoot."

Postural hypotension was present in nearly all patients studied with intravenous infusion, but could not be detected after single injec-

tions, probably because of the short duration of the action of the drug.

E. Side Effects. Yawning and a sensation of warmth were the only complaints of the patients who did not have a significant fall in blood pressure, even when Arfonad was given at a rate of 30 to 60 mg. per minute. When severe hypotension occurred, nausea, vomiting, pallor, dizziness and other signs of circulatory collapse were present. These symptoms subsided rapidly when the blood pressure was elevated to control levels either by raising the lower extremities to an angle of 90 degrees or by injection of 25 mg. of ephedrine intravenously.

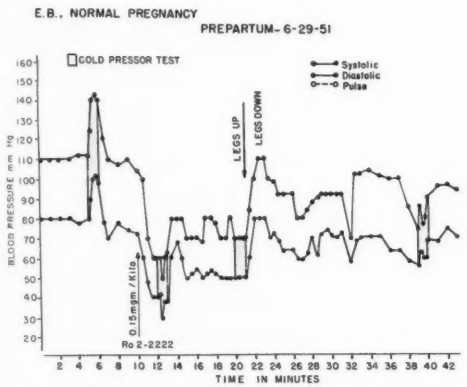

FIG. 6. This patient was one of the two who had prolonged response to a single injection of 0.15 mg. per kilogram. Note the marked pressor reaction to cold in the control period and the elimination of this reaction after Ro 2-2222.

DISCUSSION

Randall and his co-workers[1] demonstrated in animals that the blocking effects of Arfonad were exerted mostly at the ganglionic level of sympathetic and parasympathetic pathways. These authors were able to produce a blockade of transmission through the superior cervical ganglion and through the carotid sinus reflex and blockade of the vagus action on the heart. They were unable to show any neuromuscular blocking action. The ganglionic blocking and vasodepressor effects of Arfonad could be counteracted by neostigmine and ephedrine.

Sarnoff and associates[2] administered Arfonad to hypertensive patients with heart failure by intravenous drip infusion and obtained a graded reduction of arterial pressure concomitant with a fall in pulmonary venous pressure.

The present data on the vasodepression produced by Arfonad in pregnant human subjects are in close agreement with those presented by Sarnoff and his associates. In our patients who showed a fall in the blood pressure, the hypotension could be regulated to a desired level by merely changing the rate of infusion. Although in three patients there was some indication of presence of cumulative effect, in the majority, the blood pressure returned to control levels shortly after the interruption of infusion.

Sarnoff[2] observed increased cardiac output at the height of hypotension after Arfonad. In our cases, there was a decrease in the cardiac output whenever the blood pressure fell significantly. Similar reduction in cardiac output has been reported following induction of high selective spinal anesthesia in pregnant women.[5b] The discrepancy between our results and those reported by Sarnoff and his co-workers may be due to a difference in the type of patients studied. While their patients were in heart failure, presumably with a low output, ours were healthy young subjects with normal output. Further studies are in progress in order to elucidate this question.

Concomitant with the decrease in cardiac output, Arfonad evoked a significant reduction in the total peripheral resistance. This was to be expected since most of the normotensive pregnant and essential hypertensive subjects showed signs of peripheral circulatory collapse at the height of blood pressure fall. The simultaneous reduction in peripheral resistance and cardiac output suggests that in pregnant subjects Arfonad acts like spinal anesthesia by blocking neurogenic impulses to both arteriolar and venous system. This blockade probably results in pooling of blood in the venous side of the circulation, interfering with the venous return to the right heart and with right auricular filling.[5b] As in the case of spinal anesthesia, raising the legs to an angle of 90 degrees at the height of Arfonad induced hypotension was sufficient to restore the pooled blood to the systemic circulation, thus improving the cardiac

output and raising the blood pressure to control levels. The similarity between the actions of Arfonad and selective spinal anesthesia is also evidenced by their identical effects on renal hemodynamics. The hypotensive effect of spinal anesthesia is accompanied by significant reduction in the renal plasma flow with a simultaneous increase in the renal resistance.[11] The data on renal hemodynamics obtained with Arfonad[9] closely paralleled that of spinal anesthesia and showed that during the hypotensive phase the total peripheral resistance decreased while the renal resistance increased. This divergency in response of the kidneys and other segments of the vascular bed indicates that there is a difference in the mechanisms which control the circulation of blood to various areas of the body. Freis and his associates[12] have observed similar differences in their studies on the hemodynamic effects of hexamethonium.

A rise in the skin temperature of the lower extremities without a significant change in that of the upper extremities after Arfonad was observed by Green[3] and by Sarnoff and associates,[2] and is confirmed in the present study. This phenomenon, unexplained at present, would seem to indicate that in the lower extremities there is increased vasomotor tone which makes this part of the vascular bed more responsive to the effects of ganglionic blocking agents.

The present data with single injections of Arfonad show that within the range of dosage given, the hypotensive effects of this drug are not much different from those of tetraethylammonium chloride. Whether larger doses could evoke different responses cannot be stated from these observations. The vasodepressor response observed in normotensive pregnant and essential hypertensive subjects and the negligible response of normotensive nonpregnant and toxemic subjects resemble closely the results obtained with both tetraethylammonium chloride and spinal anesthesia. However, unlike tetraethylammonium chloride, Arfonad was very effective in reducing the blood pressure and blocking the vasopressor reflexes when given by intravenous drip infusion. The observations of Ulrich and coworkers[13] and of Brust and Ferris[14] have indicated that intravenous drip infusion of tetraethylammonium chloride even when given at a rate which should result in severe toxic side effects, does not produce any vasodepressor action in normotensive and hypertensive subjects. Also, the side effects peculiar to tetraethylammonium chloride are not observed after Arfonad. Thus, while the effects of Arfonad and tetraethylammonium chloride when given by rapid injection are similar, Arfonad, unlike tetraethylammonium chloride, possesses peculiar pharmacologic properties which also make it effective when given by slow intravenous infusion.

Summary and Conclusions

1. Studies on the hemodynamic effects of Arfonad were carried out on 10 normotensive nonpregnant, 20 normotensive pregnant, 10 toxemic and 16 essential hypertensive pregnant subjects.

2. Arfonad given by single intravenous injection in doses of 0.1 to 0.2 mg. per kilogram produced a significant blood pressure fall in the normotensive pregnant and essential hypertensive subjects which was parallel to the fall observed with 400 mg. of tetraethylammonium chloride. The same dosage produced a negligible blood pressure change in the toxemic and normotensive nonpregnant groups.

3. Intravenous infusion of Arfonad also resulted in a marked fall in the blood pressure of the normotensive pregnant and essential hypertensive groups. In the majority of patients, the hypotensive effect lasted for as long as the infusion continued. Toxemic and normotensive nonpregnant subjects showed much less blood pressure fall even when the rate of infusion was much higher.

4. At the height of hypotension, the cardiac output and peripheral resistance were significantly reduced, the pressor responses to cold and to Valsalva maneuver were abolished, and the skin temperature of the lower extremities rose more markedly than that of the upper extremities.

5. It is concluded that in human pregnant subjects, some of the hemodynamic effects of Arfonad resemble those of tetraethylammonium chloride or selective spinal anesthesia.

ACKNOWLEDGMENTS

The authors are indebted to Dr. John Braunstein and to Miss Mary Jane Tompkins for the cardiac output determinations.

SUMARIO ESPAÑOL

Observaciones de las propiedades hemodinámicas de un derivado de thiophanium (Arfonad) han sido hechas en sujetas normotensas embarazadas con complicaciones hipertensas del embarazo. La droga se administró mediante inyecciones intravenosas sencillas y mediante infusiones a gota intravenosas. Los efectos hipotensos de inyecciones sencillas fueron comparados a aquellos de una prueba standard de cloruro de tetraetilamonio (TEAC). Los autores observaron que los efectos hemodinámicos de Arfonad fueron similares en algunos respectos a aquellos del cloruro de tetraetilamonio o anestesia espinal. Una reducción en la producción cardíaca ocurrió cuando la presión arterial disminuyó luego de la administración del Arfonad. Los autores discuten estos efectos hemodinámicos en términos de diferencias en reacción a los agentes bloqueadores gangliónicos de los varios grupos de sujetos estudiados.

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Dye Dilution Curves in Cyanotic Congenital Heart Disease

By H. J. C. Swan, Ph.D., M.B., M.R.C.P. (Lond.), J. Zapata-Diaz, M.D., and Earl H. Wood, M.D., Ph.D.

Use of cuvette and earpiece oximeters facilitates the recording of the immediate dilution pattern of the dye T-1824 (Evans blue) in the arterial blood. In patients with venoarterial shunts the pattern of the dilution curves differs from normal. Quantitative analysis of such curves from patients with cyanotic congenital heart disease has been undertaken to establish the proportion of blood which bypassed the pulmonary circulation. The results obtained have been compared with estimates of the volume of the shunt from cardiac catheterization data and related to the arterial oxygen saturation.

AN IDENTIFIABLE substance injected almost instantaneously into the blood vessels is diluted in a specific manner by the blood stream. Nicholson, Burchell and Wood[1] used cuvette and earpiece oximeters[2] to record continuously the dilution curve of Evans blue dye in arterial blood flowing from the radial artery and through the heat-flushed ears of normal subjects and of patients with heart disease. Beard and associates[3, 4] have shown that dye dilution curves, obtained when radial or femoral arterial blood is drawn continuously through a whole-blood cuvette oximeter, are similar in contour to curves simultaneously recorded by an earpiece oximeter. Dye curves recorded by an earpiece oximeter are, therefore, an adequate qualitative guide to the dilution pattern of dye in the arterial blood.

Dye dilution curves have been obtained for patients suffering from both congenital and acquired heart disease.[1, 5, 6] In congenital defects with a venoarterial or arteriovenous shunt the basic pattern of the dye dilution curve is altered. In such conditions the morphology of the curve may indicate the presence, direction and magnitude of the shunt. The method has been extended by the technic of injection of dye by way of the cardiac catheter into the cardiac chambers and great vessels. In several cases this has permitted more accurate localization of the defect than would otherwise have been possible[7] (fig. 1). Quantitation of the volume of the shunt from dye curves of peripheral blood would be of considerable value, and Broadbent and associates[5] have reported a method of analysis of the dye curves obtained from patients with arteriovenous (left-to-right) shunts. Prinzmetal[8] reported four cases of venoarterial shunt in which he attempted to estimate the volume of the shunt from the ether and saccharine circulation times. It is the purpose of this paper to outline a method of analysis whereby the proportion of aortic flow which has bypassed the lungs via the defect can be estimated from the dye curve of patients suffering from cyanotic congenital heart disease.

From the Section of Physiology, Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester, Minn.

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Methods

Dilution curves of Evans blue dye in arterial blood were obtained from patients with cyanotic congenital heart disease. Twenty of the 25 patients whose dye curves were analyzed for this study underwent cardiac catheterization either on the same occasion or within three days of the time that the dye was recorded.

The dye curves were usually obtained according to the technic of Nicholson, Burchell and Wood,[1] but, at times, the dye was injected through a cardiac catheter, the tip of which lay in the superior vena cava. The dye curves were recorded while the patient breathed 100 per cent oxygen because the

oximeters are sensitive to changes either in oxygen saturation of blood or in concentration of dye, and changes in oxygen saturation are usually less likely when the patient is breathing 100 per cent oxygen. Continuous photographic records were obtained at a camera speed of 5 mm. per second with a photokymographic recording assembly described elsewhere.[9] Measurements of the time and concentration component of the dye curve were made directly from the photographic record.

The time components of a normal dye curve are presented in figure 2. This figure is similar to one published in an earlier report,[3] except that the term, "passage time" (PT) now replaces "clearance time," and "maximal concentration time" (MCT) has been substituted for the term "peak time." The components were defined and the average and range of values obtained in normal subjects were reported in the previous publications.[1, 3]

In this study dye curves recorded by an earpiece oximeter have been used, but the dye curves obtained by cuvette oximeter from blood flowing from a radial or other systemic artery could have been used equally well. If the latter are used, correction must be made in appearance and peak times for the interval needed for the dye to pass from the artery to the recording instrument. For some of the patients in the series to be reported dye curves had been obtained by earpiece oximeters only.

Diagnostic cardiac catheterization was carried out by utilizing strain gauge manometers, cuvette and earpiece[2] oximeters and a photokymographic recording system.[9] The calculations of the volume of shunted blood were made by the method of Burchell and Wood.[10]

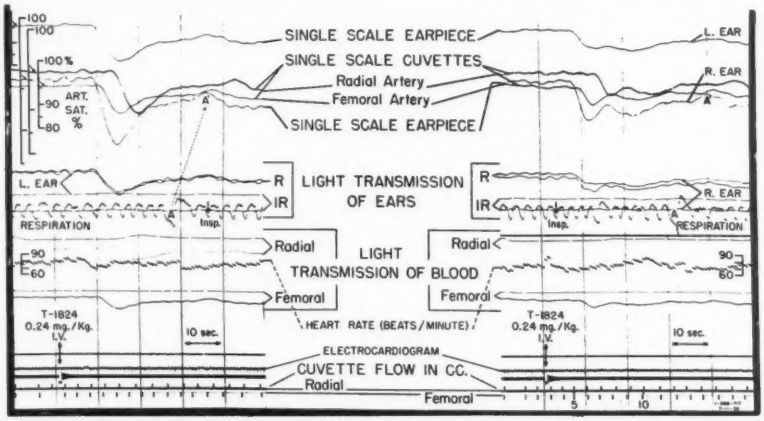

FIG. 1. Dye dilution curves recorded simultaneously from both ears and the right radial and right femoral arteries in a patient with Eisenmenger's complex. The dilution curves were recorded following injection into the pulmonary artery (*left panel*) and brachial vein (*right panel*). The contours of the dilution curves recorded from the four sites in each panel were similar. The delay in appearance of the dye at the cuvette oximeters is due to the time required for the blood to pass from the intra-arterial needle to the recording portion of the instrument. The differences in the magnitude of the recorded deflections are due to unequal sensitivities of the four oximeters. (Note oxygen calibration scales upper left corner.) The random variations in the oximeter curves before and after the injections of dye are caused by spontaneous variations in oxygen saturation resulting from changes in the veno-arterial shunt associated with the respiratory cycle. Note in both panels the rise in arterial saturation at *A'* resulting from the increased respiratory effort at *A*. Such spontaneous variations, when they occur, are the chief difficulty in the analysis of dilution curves in cases of cyanotic congenital heart disease. Note also the presence of the shunt pattern when the injection was made into a systemic vein and the absence of the shunt pattern when the injection was made into the pulmonary artery proving that the defect was proximal to the pulmonary artery.

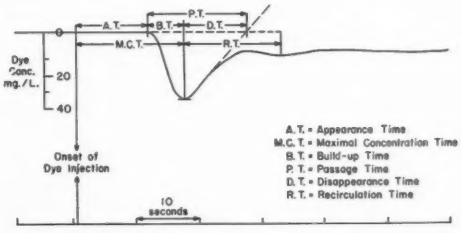

FIG. 2. Method of measurement of the circulation times and time components of a dilution curve of Evans blue dye in the arterial blood of a normal subject.

Interpretation of Dye Curves of Patients with Cyanotic Congenital Heart Disease

Among patients with cyanotic congenital heart disease without cardiac failure the dye dilution curve differs from normal in that the appearance time is usually short, although the maximal concentration time is frequently normal. In addition there is a secondary hump on the build-up slope of the dilution curve and the peak deflection is reduced. In figure 3 a dye curve obtained from a normal adult is contrasted with a curve from a 23 year old woman suffering from pulmonary hypertension and atrial septal defect who had an oxygen saturation of 82 per cent in peripheral arterial

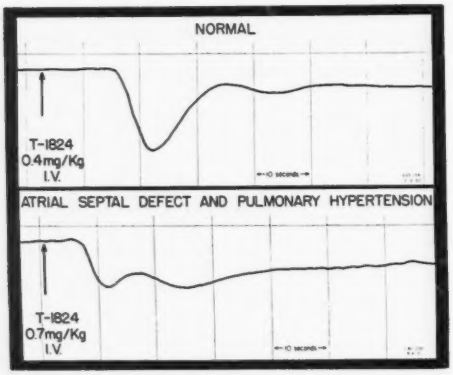

Fig. 3. Dye dilution curves in a normal subject (*upper panel*) and in a patient with cyanotic congenital heart disease (*lower panel*). Note in the *lower panel* the shorter appearance time and initial hump in concentration caused by passage of a portion of the dyed blood from right to left through the defect.

blood while at rest. This abnormal curve, which is typical of moderately severe cyanotic heart disease, can be explained by the passage of a portion of the dyed blood directly from the right atrium into the systemic circulation. As the passage of this portion of the dyed blood to the periphery is not delayed by traversing the pulmonary circuit, it arrives at the periphery earlier than the remainder of the dyed blood which passes by the more circuitous route through the lungs. This results in an appearance time which is less than normal, an initial hump in concentration due to the shunted blood, followed by, and partially fused with, the hump in concentration caused by the dyed blood which has traversed the normal circulatory pathway through the lungs.

In the following paragraphs the normal curve (the second hump, fig. 3 lower panel) representing dyed blood which has passed by way of the lungs will be referred to as the primary curve, while the "shunt" curve (the initial abnormal hump, fig. 3 lower panel) will be referred to as the secondary curve. These two curves represent the division of the dose of dye into two fractions which go by different routes to the periphery.

After the rapid injection of dye into a peripheral vein it is assumed that adequate mixing of dye and blood occurs before the intracardiac defect is reached; that is, a preferential flow of dye either toward or away from the defect is considered unlikely although such a situation could arise in the rare condition of a persistent left superior vena cava draining into the left atrium. The primary clearance of dye from the heart will result in the passage of a fraction of the total amount of dye through the defect in the same proportion as blood is passing through the defect and passage of a fraction of the total amount of dye into the lungs in the proportion that blood is passing into the lungs. In other words the relative quantities of dye passing through the shunt and through the lungs are directly proportional to the relative volumes of blood flowing by these two routes.

The dynamics affecting the dilution curves of dye in the shunted and unshunted blood differ according to the circuit taken. While the dye passing through the defect will be influenced by a number of complex dilution factors in the heart and arterial system, the dye passing through the lungs will be affected by pulmonary factors in addition. The length and capacity of different pulmonary vessels, and the rate of flow through them will determine the rate at which the dye makes the circuit and reaches the left atrium. Therefore, the primary curve (normal circulation pathway) will show a longer passage time (PT) than might be found for the secondary curve (abnormal pathway) in which the dye is cleared directly from the right side of the heart into the arterial system. For this reason comparison of maximal concentrations may not indicate

he true relative magnitude of the quantities of ye passing through the two circuits. Nevertheless, the primary and secondary curves still epresent the division of the dye into separate ractions at the intracardiac defect. They possess components in time and concentration hich together are a measure of the amount f dye which passed by each route.

Inspection of the contour of the dye curve uggested that each component could be expressed as a right-angled triangle[11] two sides f which are the build-up time and maximal concentration (fig. 4). The area of such a triangle, to be called the "build-up triangle," is equal to half the product of the build-up time and the maximal deflection. In the primary curve the maximal deflection is proportional to the maximal concentration (MC′) and may be measured in centimeters from the base line to the peak of the primary curve. In the secondary curve the maximal concentration is the distance in centimeters from the base line to the maximal deflection in the secondary curve (MC″). The peak deflection of the secondary curve may be indefinite in cases in which the shunt is small and in such cases this peak concentration is taken to be at the indentation on the main build-up slope, as shown in figure 4 (lower panel). Since absolute quantitation is not attempted, it is possible to use the measurement of concentration in centimeters, and conversion into units of concentration of dye is unnecessary. The build-up time of the secondary curve is the interval between the first appearance of the dye and the time of maximal concentration of the secondary curve (BT″). Therefore, three of the required measurements may be obtained directly from the record. However, it is necessary to estimate what the build-up time of the primary curve would have been if no shunt of dye had taken place. Because of the symmetry of dye curves it appeared possible to determine the build-up time by its relation to another variable which could be measured on the abnormal dye curve. In 42 dye curves obtained from individuals with varying cardiac outputs but no intracardiac defect a positive correlation ($r = 0.95$) was found between appearance time (AT) and maximal concentration time (MCT). The ratio AT:MCT averaged 0.56 ± 0.007.* In the abnormal dye curves the maximal concentration time was measured and from this figure the theoretic appearance time for the primary component was calculated (AT′ = 0.56 MCT). The build-up time of the primary curve was then obtained (BT′ = MCT − AT′, or BT′ = 0.44 MCT).

It is important to know the relationship between the build-up triangle and the whole curve which it is taken to represent, for the object of

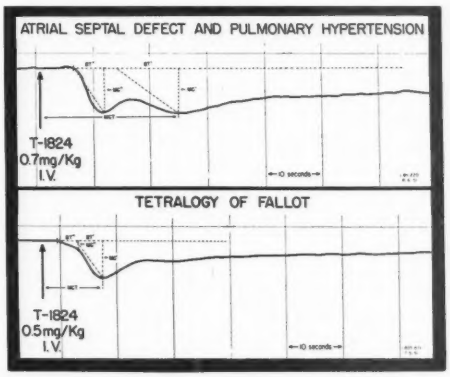

FIG. 4. Method of measurement of the build-up triangles for calculation of venoarterial shunts from dye dilution curves recorded from patients with cyanotic congenital heart disease. In the primary curve (second peak from injection) the components are *MC′*, maximal concentration, and *BT′*, build-up time. In the secondary curve (first peak) the corresponding values are *MC″* and *BT″*.

The *upper panel* is a record from a patient with a venoarterial shunt calculated by dye method to be 32 per cent of the systemic blood flow in whom the arterial oxygen saturation was 81 per cent.

The *lower panel* is a record from a 4 year old boy with tetralogy of Fallot. The shunt was calculated to be 14 per cent of the systemic flow and the arterial saturation was 93 per cent.

the method is to compare the amounts of dye in the component curves. As indicated by Warner and Wood,[11] the whole dye curve can be expressed, with reasonable accuracy, as a triangle the base of which is the passage time, with the apex at the point of maximal deflection. Analysis of 20 normal dye curves revealed a high correlation ($r = 0.97$) between passage

* The figure following the ± sign is the standard error of the mean; $N = 42$.

time and build-up time. The ratio BT:PT was 0.38 ± .006.* As the area of the whole triangle is given by the product of passage time and one half of the maximal concentration, and the concentration factor is common also to the build-up triangle, it is clear that the build-up triangle is in fact representative of the total dilution curve. Also the build-up triangle would be unlikely to reflect changes in the primary dilution curve due to concomitant pulmonary recirculation (left-to-right shunt) which not infrequently occurs in association with a venoarterial shunt.

Calculation of the Shunt. If the build-up triangles of the primary (Δ') and secondary (Δ'') dye curves are representative of the division of dye into two components with subsequent dilution in the blood stream, then the sum of both triangles indicates the total systemic blood flow. The proportion of dye passing through the shunt is obtained by the ratio of the secondary build-up triangle to the sum of both triangles or

$$\text{per cent shunt} = \frac{\Delta''}{\Delta' + \Delta''} \times 100.$$

The dye curves of 25 patients were selected for study. Those of six other patients were excluded from the series as follows: those of two who had Ebstein's disease, those of two who had tricuspid atresia in which the appearance times were abnormally short but no primary curve could be identified, and those of two who had ventricular septal defects in association with a patent ductus arteriosus with reversal of flow in which variations in arterial oxygen saturation coincident with respiration nearly obliterated the oximetric recording of the contour of the dye curve so that analysis was impossible.

Results

The results are given in table 1. In the 17 adult patients the appearance time was short with a mean value of 8.6 seconds (range: 5.2 to 14.0), the maximal concentration time was normal, 25.7 seconds (range: 14.3 to 34.8). In a series of dye curves from normal subjects, the appearance time was 14 seconds (range: 10 to 19) and the maximal concentration time, 23.9 seconds (range: 16 to 35).

The volume of the venoarterial shunt as calculated from the catheterization data in 20 of our 25 cases has been plotted against the values determined by the dye method in the same 20 cases (fig. 5). The results obtained by the two methods correlated well ($r = 0.89$); however, the volume of shunt calculated from cardiac catheterization data averaged 35 (7 to 60) per cent of systemic blood flow as compared to 26 (6 to 42) per cent calculated by the dye method. This systematic difference of 9 ± 1.5* per cent between the two methods was statistically significant ($p < 0.001$). The standard deviation of the differences between the paired determinations from the catheterization data and from the dye curve was 7 per cent of systemic blood flow or 21 per cent of the absolute shunted blood flow.

The most likely explanation for the systematic difference between the methods was that the declining concentration slope of the initially-occurring secondary curve influenced the maximal concentration of the following primary curve. This is also an important criticism of the method just outlined. If this were the case the area of the primary triangle (Δ') would be overestimated due to the inclusion of a falsely high value for maximal concentration. Therefore, final calculation would tend to underestimate the magnitude of the shunt because of a high value for the denominator in the fraction given. The figure used for the maximal concentration of the primary curve was reduced by a third as an arbitrary correction factor, thereby eliminating the systematic difference between the methods.

Although rapid sampling of blood from the various cardiac chambers by means of a whole blood cuvette oximeter increases the accuracy of calculation of shunts from catheterization data, this method of calculation still serves only to give an approximate value. In a number of the cases of ventricular septal defect with pulmonary stenosis studied, evidence of pulmonary recirculation has been found both

* The figure following the ± sign is the standard error of the mean; $N = 20$.

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TABLE 1.—*Relationship of Appearance and Maximal Concentration Times of Evans Blue Dye, the Magnitude of the Venous Arterial Shunt Calculated from Data Obtained from Cardiac Catheterization and Dye Dilution Curves, to the Levels of Arterial Oxygen Saturation in Patients With Cyanotic Congenital Heart Disease*

Patient	Age, yr.	Diagnosis	AT,* sec.	MCT,* sec.	Per cent systemic flow			Arterial O_2 per cent*
					By cardiac catheterization	By dye method before correction	By dye method after correction†	
1‡	5	Pulmonary stenosis; atrial septal defect	4.2	16.1	60	42	51	71
2	23	Tetralogy of Fallot	7.0	24.7	60	41	49	73
3	25	Tetralogy of Fallot	11.8	24.4	42	35	46	73
4	39	Pulmonary hypertension; ventricular septal defect	10.1	34.8	41	27	36	80
5	23	Pulmonary hypertension; atrial septal defect	6.3	24.7	33	32	41	81
6	28	Pulmonary hypertension; atrial septal defect; ventricular septal defect	5.2	19.3	45	40	50	81
7‡	7	Tetralogy of Fallot	5.0	14.1	56	40	50	83
8	34	Tetralogy of Fallot	9.5	26.1	39	32	41	86
9	24	Pulmonary hypertension; atrial septal defect	10.0	28.1	40	16	22	86
10	23	Tetralogy of Fallot	12.3	31.0	42	26	33	87
11‡	7	Pulmonary stenosis; ventricular septal defect	3.7	13.6	29	24	30	88
12	43	Pulmonary hypertension; ventricular septal defect	8.2	27.1	21	14	19	88
13‡	3½	Pulmonary stenosis; ventricular septal defect	4.6	12.8	33	32	41	89
14	28	Ebstein's disease (?)	7.0	27.4	26	19	26	89
15	20	Pulmonary stenosis; atrial septal defect	6.8	14.3	31	24	32	90
16	16	Pulmonary stenosis; ventricular septal defect	9.3	23.0	25	20	26	90
17‡	4½	Pulmonary stenosis; ventricular septal defect	4.9	13.3	25	19	25	91
18	10	Pulmonary hypertension; ventricular septal defect	4.3	15.1	19	16	22	92
19‡	4½	Tetralogy of Fallot	3.5	11.1	16	14	20	93
20‡	3½	Pulmonary stenosis; ventricular septal defect	4.0	10.0	7	6	8	95
21§	25	Tetralogy of Fallot	5.2	23.2		45	56	66
22§	49	Pulmonary arteriovenous fistula (?)‖	14.0	32.0		38	48	68
23§	37	Atrial septal defect; ventricular septal defect (?)	9.0	31.0		42	52	76
24§	41	Eisenmenger's syndrome (?)	7.4	25.6		33	42	78
25§	52	Eisenmenger's syndrome (?)	6.4	19.8		19	25	87

* AT = Appearance time; MCT = Maximal concentration time; arterial O_2% = Oxygen saturation in arterial blood.

† Dye values corrected to agree with cardiac catheterization estimate by reducing the area of the primary triangle by one third.

‡ Under light Avertin anesthesia.

§ Patients 21 to 25 were not studied by cardiac catheterization.

‖ Necropsy on this patient revealed bronchiectasis, emphysema with pulmonary vascular sclerosis, grade 3, but no fistulous communication could be demonstrated. It is probable that the abnormal dye curve is caused by the passage of some blood through the bronchiectatic region (AT = 14 seconds) followed by a slower rate of flow by way of the normal channels in the emphysematous lung.

in the contour of the dye curves obtained and in the cardiac catheterization data. Therefore, it may be difficult to obtain adequate samples to establish the true value for oxygen saturation

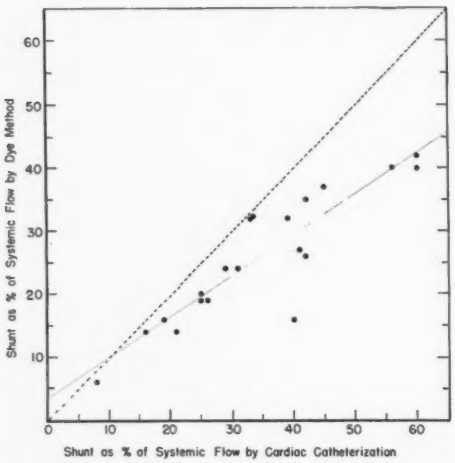

FIG. 5. Comparison of the magnitude of venoarterial shunts as calculated by the cardiac catheterization and dye methods. The broken line represents identity while the fine line is the regression: $Y = 3.5 + 0.65X$, where X is the shunt as estimated from the cardiac catheterization data and Y the shunt calculated by the dye method. The standard error of the coefficient of regression ($b = 0.65$) was 0.07 and the standard deviation of any single determination from the calculated line was 6.6 per cent of systemic flow. The correlation between the methods was 0.89.

of mixed venous blood and it is likely that a good proportion of the variability between the methods was due to error in the determination from the catheterization data. In spite of such difficulties a relatively good agreement has been found between the estimates of the shunt by the dye method (corrected) and from data collected by cardiac catheterization.

In figure 6, left, the oxygen saturation of arterial blood of the patients at rest is plotted against the per cent of the shunt as estimated by the dye method (corrected). If the volume of the shunt is less than 30 per cent of the systemic blood flow, then the degree of oxygen desaturation is not severe. If the volume of the shunt exceeds 40 per cent of systemic blood flow, then a marked fall in oxygen saturation occurs. It might be expected that in the larger shunts the low oxygen content of the arterial blood passing to the periphery results in the return to the heart of grossly desaturated blood, part of which again passes to the arterial system by way of the defect. It is probable that such a cycle underlies the marked fall in oxygen saturation of arterial blood in the presence of shunts of more than 35 per cent of systemic

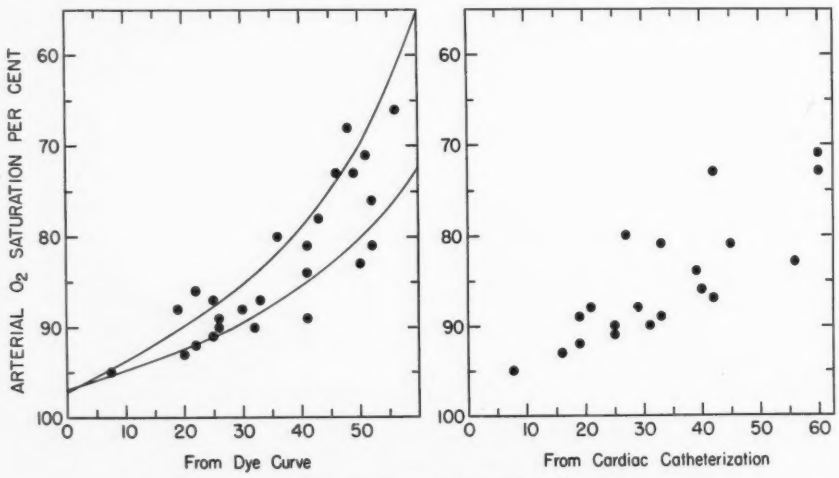

FIG. 6. The relation of arterial oxygen saturation to the magnitude of the venoarterial shunt. In the *left panel* two theoretically derived curves have been drawn relating oxygen saturation to volume of shunt when constant systemic flow and arteriovenous oxygen difference were assumed. The upper curve assumes an arteriovenous difference of 5 cc. of oxygen per 100 cc. of blood; the lower, a difference of 3 cc. of oxygen. It is realized that factors other than volume of shunt affect the arterial saturation but the present data do not permit a precise analysis of this relationship.

In the *right panel* the degree of oxygen was derived from data obtained at cardiac catheterization.

blood flow. However, the data available do not permit adequate analysis of the many interrelated factors governing the relationship between oxygen saturation and the magnitude of the shunt. The relationship just proposed was not evident in a comparison of oxygen saturation and per cent shunt calculated from the hemodynamic data (fig. 6, right), but it should be pointed out that several of the patients with severe cyanosis did not undergo catheterization and points of comparison in this important low range of oxygen saturation were not available.

For five patients a second dye curve was obtained 8 days to 23 months after the first. Good agreement was found between the calculation of the volume of the shunt on successive occasions. Details of the findings are given in table 2.

concentration of the primary curve is not entirely satisfactory and a more theoretically accurate determination could be made.* However, the shunt as calculated from the catheterization data, the standard of comparison in this study, is itself open to considerable error[12, 13] and further elaboration of the dye method does not at present seem justified.

Dye curves were recorded simultaneously from more than one site for a number of patients. Suitable curves from both ears or from one ear and radial artery were obtained from nine patients. The percentage of blood passing through the shunt did not differ by more than 5 per cent when determinations from two earpieces were compared or by more than 8 per cent when determinations of earpiece and cuvette were compared. The error of measurement is, therefore, relatively small. This accuracy of measurement is clearly dependent on the quality and dimensions of the dye curves obtained. If the oximeter record of the arterial oxygen saturation is stable, this can be achieved with a small dose of dye by using a highly sensitive recording instrument, but if there are variations in arterial oxygen saturation as fre-

TABLE 2.—*Reproducibility of Hemodynamic Measurements from Dye Dilution Curves Recorded from Five Patients Studied on Two Different Occasions*

Patient	Time between studies	First occasion				Second occasion				Remarks
		AT*	MCT*	% shunt	O_2%*	AT*	MCT*	% shunt	O_2 %*	
2	4 mo.	7.0	24.7	41	73	7.9	24.2	40	78	After Blalock operation
3	24 mo.	11.8	24.4	35	73	8.2	22.6	35	91	After Blalock operation
4	16 days	9.4	29.0	26	84	10.1	34.8	27	80	Second occasion catheterization
6	8 days	5.2	19.3	40	81	5.9	18.2	42	81	
8	4 mo.	9.5	26.1	32	86	9.8	27.4	25	90	After Blalock operation

* AT = Appearance time; MCT = Maximal concentration time; O_2% = Oxygen saturation of arterial blood.

COMMENT

The method described in the earlier paragraphs evolves from the concept of division of the dye into two separate fractions which are proportionate to the volume of blood passing into the arterial system by different routes. The shunt calculated by the dye method correlates well with that obtained from cardiac catheterization data although an empiric correction factor would have to be used to eliminate a systemic difference between the two methods. Indeed the inclusion of such a correction factor would appear necessary from simple inspection of normal and abnormal dye dilution curves because the disappearance slope is always less steep than the build-up slope and some influence of the secondary curve on the primary is to be anticipated. A fixed value of 0.66 for the correction factor for the maximal

* Making the assumption that the declining slopes of concentration of the primary and secondary dilution curves paralleled each other, a semilogarithmic plot of the declining slope of the primary curve was made from which a more accurate estimate of the influence of the secondary curve on the maximal concentration of the primary curve (MC') was obtained. In a few curves it was possible to replot the declining slope of the secondary (initial) curve and so to estimate the true value of MC'. Introduction of these theoretically desirable corrections would appear to complicate the procedure unduly for practical purposes.

quently occur in such patients, then a large dose of dye should be used. This difficulty is illustrated in figure 1; a moderate fluctuation in arterial oxygen saturation coincident with respiration renders identification of the points of maximal concentration uncertain. In other records the fluctuations have been even greater. The average dose of dye used for the 25 patients studied was 0.60 mg. per kilogram of body weight with a range of from 0.17 to 1.06 mg. per kilogram.

shunt, when the volume of shunt was determined from two dye curves obtained at different times during cardiac catheterization.

It will be recalled that the dye curves were recorded while the patient was breathing 100 per cent oxygen, but the catheterization data were usually obtained while the patient was breathing room air. The basis for the comparison of the percentage shunt determined from the cardiac catheterization data and that by the dye method rests on the finding that veno-

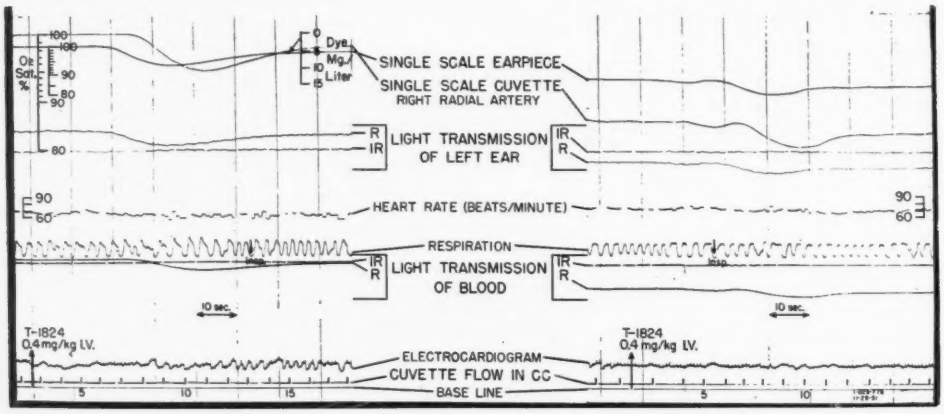

FIG. 7. Alteration in the direction of a shunt caused by change in the oxygen content of the inspired air in a 30 year old woman with atrial septal defect, pulmonary hypertension and cardiac failure. The curve in the *left panel* was obtained while the patient was breathing 100 per cent oxygen, in the *right panel* while she was breathing room air. All components of the curves are prolonged, associated with the low output of cardiac failure. The disappearance times of the dye curves in the *left panel* are disproportionately prolonged indicating the presence of a left-to-right shunt. The curves in the *right panel*, however, show a short appearance time and an abnormal initial hump indicating a shunt in the right-to-left direction which was not present when the patient was breathing 100 per cent oxygen. The scale of sensitivity to dye applies only to the *left panel*. When the patient was breathing room air the arterial saturation was 84 per cent. Due to this desaturation a second calibration of the cuvette oximeter to dye was not obtained.

A high degree of repeatability was demonstrated on retesting patients after an interval (table 2). The percentage volume of the right-to-left shunt calculated in three patients differed little after a Blalock operation for tetralogy of Fallot from the preoperative volume although the oxygen saturation of arterial blood was elevated and clinical improvement had occurred. The contour of the dye curves of these patients also indicated the presence of pulmonary recirculation. Two additional patients, data on whom were not included in table 2 also showed no difference in the volume of the arterial shunts are usually unchanged when the patient breathes 100 per cent oxygen.[14] However, in a few patients the magnitude of the shunt was altered or the direction reversed when the patient breathed 100 per cent oxygen.[15] Dye curves obtained for such a patient are shown in figure 7. Also we have demonstrated intracardiac arteriovenous shunts in a few patients when they were breathing 100 per cent oxygen which could not be detected when they were breathing room air. In these patients the oxygen probably lowers the pulmonary resistance and thus permits an increase in the

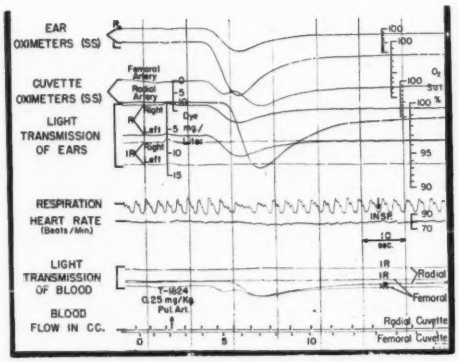

FIG. 8. Difference in dye curves from a 44 year old woman suffering from patent ductus arteriosus and pulmonary hypertension. Dilution curves were recorded from both ears and right radial and right femoral arteries. The appearance and build-up times of the curves obtained from the ears and radial artery were normal but the disappearance time was slightly prolonged consistent with a small left-to-right shunt. The curve from the femoral artery, however, showed a short appearance time and an abnormal initial hump, demonstrating the early passage of a portion of dyed blood to the lower part of the body by way of the ductus. The oxygen saturation of the femoral artery blood (83 per cent) was lower than that of a simultaneously withdrawn radial artery sample (94 per cent).

TABLE 3.—*The Change in Magnitude of the Veno-arterial Shunt Calculated from Cardiac Catheterization Data on Breathing 100 Per Cent Oxygen*

No.	Diagnosis	Shunt per cent of systemic flow	
		Air	100% O_2
1	Pulmonary stenosis; atrial septal defect	60	68
2	Tetralogy of Fallot	60	63
5	Pulmonary hypertension; atrial septal defect	33	38
6	Pulmonary hypertension; atrial and ventricular septal defects	45	32
8	Tetralogy of Fallot	39	31
16	Pulmonary stenosis; ventricular septal defect	25	17
18	Pulmonary hypertension; ventricular septal defect	19	22

Mean change = 1 per cent (change not significant).

proportion of blood entering the pulmonary artery.[15] It should be noted that in cases of patent ductus arteriosus with pulmonary hypertension of a degree to cause reversal of flow through the ductus, the dye dilution curves recorded from the right radial and femoral arteries may differ; the femoral curve indicating a right-to-left shunt and the radial no shunt or a shunt in the left-to-right direction (fig. 8).

In the results just reported data obtained by cardiac catheterization were collected for the most part while the patient was breathing room air, but the majority of dye curves were obtained while the patient was breathing 100 per cent oxygen. When the catheterization data permitted, the volume of shunt when the patient was breathing 100 per cent oxygen was also calculated (table 3), and in the present series did not differ systematically from the shunt obtained during the breathing of air. The differences observed may be within the error of the method. Nevertheless, in a few cases, the possibility does exist that the volume of the shunt may have altered between the time of collection of the catheterization data and the recording of the dye dilution curve.

Evans blue dye dilution curves then can be used to indicate the presence, direction and magnitude of veno-arterial shunts in cyanotic congenital heart disease. In suitable cases it is possible to demonstrate changes in the magnitude and even direction of shunts caused by different procedures. Changes in magnitude of shunts as calculated by the dye method may be more nearly accurate than the absolute volume of the shunt although satisfactory agreement with estimates from the cardiac catheterization data has been obtained in this series. Estimates from the cardiac catheterization data are, however, by no means ideal standards of comparison and calculation from dye dilution curves may be more representative of the volume of shunt at a given moment than the calculations from cardiac catheterization data obtained over a period of several minutes. The degree of correlation obtained between the amount of arterial oxygen desaturation and the relative volume of the shunt as calculated by the dye method lends credence to this concept.

SUMMARY

Dilution curves of Evans blue dye in the arterial blood were recorded for 25 patients

with cyanotic congenital heart disease. The first appearance of the injected dye at a recording oximeter attached to the ear was earlier than that for normal persons. An abnormal hump was found on the build-up slope of the curve which was taken to represent dye which had by-passed the pulmonary circuit by way of an intracardiac defect.

Certain features of the dye curve could be measured and it was possible to calculate the proportion of dye which had passed through the intracardiac defect. This indicated the percentage of the total systemic blood flow which had been shunted from the venous system.

For 20 patients data from cardiac catheterization were available which made it possible to compare the volume of the shunt as calculated from the dye curve and from cardiac catheterization data. A systematic difference amounting to 9 per cent of the systemic flow was found between the methods. The standard deviation of the differences between determinations of venoarterial shunts by cardiac catheterization and dye dilution methods was 7 per cent of the systemic flow. For the dye curve method a high degree of repeatability was demonstrated.

The arterial oxygen desaturation was related to the volume of the shunt. When the shunt exceeded 35 per cent of the systemic blood flow, severe oxygen desaturation was present when the patient was at rest.

The method represents a relatively simple and adequate technic for determining the magnitude of the shunt in cases of cyanotic congenital heart disease. From some patients, however, curves have been obtained which do not permit quantitation, either due to spontaneous fluctuation in arterial oxygen saturation sufficient to obscure the dye curve or to dye curves, the components of which were too poorly defined to permit measurements of the type required for the calculation.

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Sumario Español

El uso de un cuvette y un oxímetro de oído facilita el registro del patrón de dilución inmediata del tine T-1824 (azul de Evans) en la sangre arterial. En pacientes con shunts arteriovenosos el patrón de las curvas de dilución difiere de lo normal. Analisis quantitativo de las curvas obtenidas en estos pacientes con enfermedad cianótica congénita del corazón ha sido determinado para establecer la proportión de sangre que circunda la circulación pulmonar. Los resultados obtenidos han sido comparados con estimados del volumen del shunt según datos de caterización cardíaca y relacionados a la saturación de oxígeno arterial.

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Measurement of Vasoconstrictor Tone in the Extremities in Hypertension

By Henry J. Kowalski, M.D., Sibley W. Hoobler, M.D., Sc.D., S. Donald Malton, M.D., and Richard H. Lyons, M.D.

Tetraethylammonium (TEA) given intravenously decreases peripheral vascular resistance. The magnitude of the decrement is related directly to the prevailing level of neurogenic vasomotor tone. TEA was administered to hypertensive and normotensive subjects. The decrements in resistance of the foot did not differ between the two groups. The decrements of the forearm also did not differ. These findings suggest that the prevailing level of neurogenic vasomotor tone in the extremities is not increased in hypertension.

STUDY of the altered hemodynamics in essential hypertension indicates a significant increase in the total peripheral resistance of the arteriolar bed.[1, 2] The nature of the arteriolar hypertonus remains obscure, but evidence suggests that in some portions of the circulation it may be functional and reversible.[2, 3]

Using the venous occlusion plethysmograph, several workers have attempted to evaluate the role played by the blood vessels of the extremities in the increased vascular resistance. Most have agreed that there is an increased peripheral resistance in these vascular beds.[2, 4, 5] However, Abramson and Fierst suggested that the forearm blood vessels might not share in the elevated peripheral resistance since they found an increased blood flow in the forearm of their hypertensive patients.[6]

The extent to which increased vasomotor tone* contributes to the elevated peripheral resistance has been investigated by Pickering[5] and Prinzmetal and Wilson.[4] When vasoconstrictor tone was decreased reflexly by body heating or by paravertebral block, or where reactive hyperemia was employed, the peripheral resistance in hypertensives did not fall to the levels seen in normotensives. It was suggested, therefore, that the vasomotor tone to the peripheral vessels was not increased in hypertension.

The observation that tetraethylammonium, a drug capable of inhibiting ganglionic transmission of vasomotor tone, reduced the blood pressure of hypertensive subjects more than that of normotensives raised again the question of the presence of increased vasomotor tone in this disease, and the development of such a chemical blocking agent suggested its possible utilization for the measurement of vasomotor tone in the human subject. The present work was undertaken (1) to estimate the vascular resistance in the foot and forearm of hypertensives, and (2) to evaluate a method for measuring vasomotor tone using tetraethylammonium chloride.

Methods

The plethysmographic technic employed, the preparation of the patient, and the calculation of the data were similar to the methods described in a preceding paper[8] with the following exceptions: (1) Dosage of tetraethylammonium was estimated on the basis of body weight and approximately 3.0 mg. per pound (1.36 mg. per kilogram) was administered intravenously in each experiment. The range in weight of the hypertensive and control groups was similar and consequently the average dose of tetraethylammonium was comparable. (2) Blood flow in the homolateral forearm and foot were measured simultaneously in most instances. A number of patients were studied on two or three occasions and the data, marked with an asterisk in table 1

From the Department of Medicine, University of Michigan Medical School, Ann Arbor, Mich.

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* By vasomotor tone we mean the specific contribution to arteriolar tonus mediated over sympathetic ganglionic pathways.

epresent the mean of the separate determinations. 3) Pressure in the collecting cuff was determined by the optimum inflow curve obtained, which was usually 15 to 20 mm. below diastolic blood pressure, and this pressure was then utilized throughout the experiment. In most of the hypertensive patients, the decline in pressure induced by tetraethylammonium was not sufficient to lower diastolic blood pressure below the collecting cuff pressures, but occasionally this did occur. In such instances it is possible that an artefact may have been produced by the prevention of diastolic back flow,[9] with the result that the flow as measured may be slightly higher than the true flow.

As in the previous report, blood flow values represent an average of five consecutive readings, either just before administration of tetraethylammonium or at the time of maximal response. Mean blood pressure likewise represents average values taken by the auscultatory method before and during the time of maximal observed blood flows. Peripheral vascular resistance to blood flow was calculated in arbitrary units by the following formula:

$$\frac{\text{Mean blood pressure (mm. Hg.)}}{\text{Mean blood flow (cc./100 cc. limb volume/min.).}}$$

The mean blood pressure was arbitrarily taken as one-half the sum of average systolic and diastolic readings over the period of observation.

The normotensive control subjects were patients hospitalized for a variety of reasons but exhibiting no symptoms or signs of peripheral vascular disease. The hypertensives were patients with the clinical diagnosis of "essential hypertension."

Results

A summary of the experimental data is found in table 1.

I. *Observations in the Resting State*

A. Foot. Resting blood flow to the foot was slightly reduced in the patients with hypertension (H. M.* 1.71 cc.; N. M.† 2.06 cc.). The difference between these means could have been a chance occurrence.

Peripheral resistance was significantly elevated in the hypertensive subjects. Their mean value of 129 units was approximately double the normotensive mean of 62.1 units.

B. Forearm. Forearm blood flow was slightly but not significantly higher in the hypertensives (H. M. 3.21 cc.; N. M. 2.84 cc.).

The hypertensive subjects had an elevated resistance to the flow of blood in the forearm. The means were 58 units in the hypertensive subjects and 40.7 units in the normotensives. The probability of this difference between these respective means occurring by chance alone was slightly less than 1 out of 20.

II. *Observations with Tetraethylammonium*

A. Estimation of Vasomotor Tone with Tetraethylammonium. (1) The administration of tetraethylammonium is usually followed by a drop in blood pressure and an increase in peripheral blood flow. The peripheral resistance (calculated by dividing half the sum of the systolic and diastolic pressure by the blood flow) decreases. The magnitude of the decrease in peripheral resistance after tetraethylammonium appears to be determined by the level of vasomotor tone at the time the drug is given. In the experiments reported in table 2, increasing vasomotor tone was found to enhance the drop in peripheral resistance after tetraethylammonium; and, conversely, decreasing vasomotor tone was found to decrease the drop in peripheral resistance following autonomic blockade with tetraethylammonium.

The peripheral resistance dropped 79 per cent in subject G. M. (table 2) during "normal" conditions. On a subsequent occasion vasomotor tone was decreased by reflex body heating, accomplished by placing arms and trunk in a body bake for about 45 minutes. The administration of tetraethylammonium now was followed by a decrease in peripheral resistance of only 28 per cent.

In subject W. H. the response to tetraethylammonium after body heating was a drop in peripheral resistance of 9 per cent. Subsequently, when reflex vasoconstriction was induced by immersing hands in ice water, tetraethylammonium administration resulted in a peripheral resistance decrement of 74 per cent.

In the remaining two experiments reflex cooling was similarly found to increase the drop in peripheral resistance after autonomic blockade with tetraethylammonium.

(2) The response of the local vascular bed under scrutiny is the important determinant in the peripheral resistance response to tetra-

* H.M. = Hypertensive Mean.
† N.M. = Normotensive Mean.

TABLE 1.—*Changes in Blood Flow and Vascular Resistance after Tetraethylammonium in Hypertensive Subjects Compared with Normotensive Controls*

Name	Sex	Age	Blood Pressure		Foot				Forearm			
					Blood Flow		Peripheral Resistance		Blood Flow		Peripheral Resistance	
			$\frac{S. + D.}{2}$	Change after TEA %	Control cc./min.	Change after TEA %	Control	Change after TEA %	Control cc./min.	Change after TEA %	Control	Change after TEA %
Normotensive Control												
J. B.*	F	36	87	−5	1.4	+193	63	−66	3.9	+10	22	−12
G. T.*	M	49	99	−4	2.0	+145	53	−65	3.8	−2	30	−9
D. K.*	F	40	94	+3	1.2	+700	53	−87	2.3	+56	41	−30
D. D.*	F	24	96	−3	1.5	+890	72	−67	4.6	+4	21	−6
E. P.*	M	43	98	+9	1.3	+260	85	−69				
F. C.*	M	37	85	+2	3.9	+202	31	−66	2.4	+130	37	−49
L. H.	F	31	96	−10	1.7	+118	56	−58				
B. B.*	F	35	104	−7	1.3	+368	78	−84	1.4	+20	72	−22
H. T.	M	21	92	+11	4.2	+185	22	−61	1.2	+67	77	−38
T. G.	M	36	100	−8	2.1	+367	48	−80				
S. M.	M	24	101	+4	1.2	+941	84	−90	3.0	+80	33	−32
J. B.	M	37	91	−3	3.8	+124	24	−56				
O. J.	M	31	90	−10	2.9	+179	31	−68				
F. H.*	F	34	92	−5	3.1	+145	36	−63	3.0	−7	32	0
E. O.*	F	40	93	−8	1.1	+2	88	−90	2.2	+53	43	−35
B. B.*	F	38	97	+5	3.4	+9	32	0	1.3	+23	77	−14
D. S.*	M	24	92	−3	1.6	+245	64	−75	2.4	+14	38	−13
M. M.	F	45	99	−24	0.7	+128	142	−67	2.8	+28	35	−35
E. D.	M	24	90	−18	0.8	+260	113	−76	2.8	+14	32	−16
A. C.	M	36	116	−14					5.5	+38	21	−38
Normotensive Mean				−4	2.06	+287	62.1†	−68	2.84	+35	40.7‡	−23
Essential Hypertension												
M. A.*	M	41	192	−17	3.3	+218	60	−72	5.1	+59	38	−47
D. C.	F	42	202	−37	1.2	+333	168	−85	3.2	−6	63	−31
S. M.	M	39	188	−30	1.2	+383	157	−78				
W. K.*	M	36	151	−15	2.5	+30	62	−79	1.6	+13	113	−28
H. B.	M	32	179	−27	1.1	+163	161	−72	2.9	+65	61	−55
L. K.*	F	48	182	−26	0.8	+840	231	−92	3.2	0	60	−24
L. W.*	F	36	175	−14	2.0	+820	92	−90	3.0	+50	59	−36
L. D.*	M	46	169	−45	0.6	+290	288	−83				
M. D.*	M	29	166	−14	0.7	+918	233	−91	3.2	+28	53	−32
N. B.	F	29	158	−30	1.4	+193	113	−76	5.1	−24	31	−10
B. R.*	F	49	173	−14	1.3	+231	133	−74	3.9	+25	47	−30
H. G.*	M	46	152	−5	3.8	+82	40	−47	2.7	+118	58	−53
R. W.	M	37	144	−5	1.1	+736	131	−89	3.7	+5	39	−5
F. D.	F	34	129	−8	3.3	+340	39	−27	3.6	+83	36	−49
C. S.	M	45	149	−17	1.9	+395	79	−82				
V. B.*	F	48	157	−21	1.9	+132	83	−71	1.9	+26	87	−32
E. D.	F	46	144	−6	0.9	+622	160	−87				
M. S.*	F	53	146	−4	2.0	+180	79	−55	2.1	+13	72	−17
D. R.	F	45	161	−48	0.8	+1187	205	−95				
D. D.	F	32	136	−16	2.4	+290	57	−77				
Hypertensive Mean				−20	1.71	+414	129†	−76	3.21	+33	58‡	−32

† Means differ significantly at 0.1% level.

‡ Means differ significantly at 5% level. No other differences between normotensive and hypertensive means were statistically significant. S = Systolic. D = Diastolic.

All values for blood flow and peripheral resistance are referred to 100 cc. of limb volume per minute and are calculated as described in the text. Forearm and foot blood flow were performed simultaneously. In those instances where subjects were studied more than once (indicated by asterisks) peripheral resistance is the mean of ratios for several pressure-flow determinations calculated by averaging the separate quotients. Therefore such mean resistances multiplied by the flows will not equal mean blood pressures.

ethylammonium despite the fact that blood pressure and blood flow may both change. If this contention is correct, peripheral resistance should not change in sympathectomized extremities after tetraethylammonium administration. Experiments in table 3 were performed on subjects with sympathectomized extremities. Although alterations in blood flow and in blood pressure were noted after autonomic blockade with tetraethylammonium, the slight shifts in peripheral resistance of plus 3 per cent, 0.0 per cent, plus 10 per cent, and plus 1 per cent are not deemed significant.

TABLE 2.—*Peripheral Resistance Response to Tetraethylammonium (TEA) at Varying Levels of Vasomotor Tone*

Subject	Status	Before TEA		After TEA		Level of Vasomotor tone	Observed Change in PR
		BP* / F†	PR‡	BP / F	PR		
G. M.	Control	100 / 1.5	67	92 / 6.5	14	"Normal"	−79%
	After reflex body heating	108 / 8.4	12.8	89 / 9.8	9.1	Decreased	−28%
W. H.	After reflex body heating	105 / 9.4	11.2	99 / 9.7	10.2	Decreased	−9%
	After reflex cooling	101 / 2.2	44	105 / 9.3	11.3	Increased	−74%
A. A.	Control	93 / 3.2	29	70 / 4	17.5	"Normal"	−39.5%
	After reflex cooling	98 / 12	81.5	106 / 7.2	14.8	Increased	−82%
E. Mc.	Control	96 / 19	50.4	96 / 6.2	15.5	"Normal"	−69.2%
	After reflex cooling	95 / 0.7	136	86 / 6.6	13	Increased	−90.5%

* BP = Blood Pressure $\frac{S. + D.}{2}$

† F = Peripheral Blood Flow.

‡ PR = Peripheral Resistance.

Table presents the response to 500 mg. of TEA intravenously in volunteer subjects under "normal" conditions on one day and following a reflexly induced change in resting circulation on a subsequent day. Vasomotor tone to the foot was reduced by placing arms and trunk in a body bake for 30 to 45 min. before beginning study. Reflex vasoconstriction was induced by immersing hands in ice water for a sufficient period to produce plethysmographic evidence of vasoconstriction in the foot.

It will be noted that the response to TEA was proportional to the initial magnitude of vasomotor tone.

B. Responses to Tetraethylammonium in Hypertensive and in Normotensive Subjects. The administration of tetraethylammonium was followed by a marked and significant drop in blood pressure of the hypertensive subjects. The mean decrease was 20 per cent with a range extending from 4 to 48 per cent. Six of the 20 normotensive subjects developed slight increase in blood pressure but the mean change was a decrease of 4 per cent.

(1) Foot. Blood flow was found to increase significantly in both groups. The mean increase in blood flow after tetraethylammonium was 287 per cent over control values in the normotensive population, and 414 per cent in the hypertensive population.

The peripheral resistance decreased in both groups. The mean decrease in the normotensive subjects of 68 per cent did not differ statistically from the mean decrement of 70 per cent found in the hypertensive subjects.

(2) Forearm. Forearm blood flow increased 35 per cent in the normotensives. The hyper-

tensives likewise developed an increased flow of blood to the forearm (33 per cent).

Peripheral resistance dropped in the forearm of the normotensives. The mean decrease was 23 per cent. Administration of tetraethylammonium was also found to decrease the resistance to the flow of blood in the hypertensive subjects. The mean change was minus 32 per cent. The difference between these means (32 per cent, H. M., 23 per cent, N. M.) was not found to be significant, and may well have been due to chance alone.

TABLE 3.—*Effect of Change of Blood Pressure on Peripheral Blood Flow in the Sympathectomized Extremity*

Subject	Extremity		Mean BP (mm. Hg.)	Blood flow (cc./100 cc. limb)	Peripheral Resistance (Mean BP/Blood Flow)
J. S.	Foot	Before TEA	97	7.0	13.0
		After TEA	74	5.5	13.4
		% Change	−23	−21	+3
C.G.	Foot	Before TEA	110	2.8	39.4
		After TEA	87	2.2	39.6
		% Change	−21	−21	0
B.O.	Foot	Before TEA	188	2.0	94.0
		After TEA	145	1.4	103.0
		% Change	−23	−30	+10
O. S.	Hand	Before TEA	84	5.8	14.5
		After TEA	50	3.4	14.7
		% Change	−40	−42	+1

300–500 mg. TEA was administered intravenously in these experiments. Since the extremity had been sympathectomized the drug could not alter arteriolar caliber. Peripheral vascular resistance remained relatively constant despite considerable fluctuation in blood pressure and blood flow.

Discussion

The data reported here indicate that the amount of blood flowing to the foot and to the forearm of the hypertensive subjects studied does not differ from that amount supplying the respective vascular beds in normotensive individuals. Foot blood flow was slightly lower in the hypertensives, and forearm blood flow was slightly higher, but, as indicated above, the discrepancy from the respective normotensive value was not "significant." The resistance to this flow of blood, however, was significantly higher in both the foot and forearm of the patients with hypertension.

No similar study of foot blood flow with the plethysmograph has been made in hypertensives. However, the results of our observations agree with those of Stewart and co-workers[10] who found a slight reduction of blood flow to the skin of the lower extremities in hypertensive patients by means of a calorimetric technic.

The demonstration of increased resistance to blood flow in the forearm in the present work is contrary to the conclusions reached by Abramson and Fierst[6] who did not find elevated vascular resistance in the forearm, but our data are in accord with the observations of other workers.[4, 5]

Implicit in our use of the pressure-flow relationship is the concept that flow varies directly with pressure, or restated, the formula, $R = P/F$, must be applicable at all levels of pressure. In this connection a re-examination of the data in table 3 from a different point of view will be of interest. These individuals with sympathectomized extremities developed drops in pressure after tetraethylammonium ranging from 21 to 42 per cent at initial levels of pressure which ranged from 84 to 188 mm. Hg. If flow varied directly with pressure there would be similar reductions in blood flow and the quotient of pressure divided by flow (the peripheral resistance) should remain constant. Such was the case. Consequently we believe that changes in peripheral resistance can be compared between hypertensives and normotensives despite the greater reductions in pressure the former experience after autonomic blockade.

These observations of the relationship of pressure and flow are in good agreement with the conclusions of Wilkins and Eichna[11] that vascular resistance at different levels of blood pressure can be determined by dividing pressure by flow.

The administration of tetraethylammonium is followed by a decrease in peripheral resistance. The magnitude of this decrease can

be modified by altering the level of vasomotor tone. Increasing tone by reflex cooling (which induces vasoconstriction) increases the resistance decrement following tetraethylammonium administration. Decreasing tone, for instance, body heating, had the opposite effect. The relationship of the level of vasomotor tone to the magnitude of the peripheral resistance decrement suggests that autonomic blockade by tetraethylammonium may be used to determine the nature of the increased peripheral resistance in hypertension.

Peripheral resistance reductions were expressed in a percentage manner since this takes into account the difference in initial values. The percentage decrease in resistance to blood flow in the foot was essentially the same in the normotensives and in the hypertensives. Since the magnitude of the peripheral resistance decrement was the same for both groups it would appear that neurogenic vasomotor tone to the foot is not significantly increased in hypertension. The decrement of peripheral resistance in the forearm was also similar in both hypertensives and normotensives. Here then, as in the foot, neurogenic vasomotor tone does not appear to be increased in hypertension.

Our observations thus confirm the findings of Pickering[5] and of Prinzmetal and Wilson.[4] These workers estimated peripheral vasomotor tone by observing the increases in blood flow to extremities after paravertebral block or reflex body heating. Supernormal blood flow increases were not found in the hypertensives, as would be expected if they had increased vasomotor tone. We are therefore inclined to the opinion that in the subjects we studied normal ganglionic transmission of vasomotor tone was present and was superimposed on an underlying vascular hypertonus, the nature of which remains obscure.

Conclusions

Employing the venous occlusion plethysmograph and autonomic blockade with tetraethylammonium, evidence is presented which indicates that: (1) The vascular resistance to the foot and forearm is increased in hypertension; (2) the peripheral resistance decrement to tetraethylammonium is determined by the prevailing level of vasomotor tone, and (3) the prevailing level of neurogenic vasomotor tone in the extremities was not found to be increased in patients with hypertension.

Summary

The effect of the intravenous administration of tetraethylammonium on the peripheral resistance of the extremities is influenced by the prevailing level of neurogenic vasomotor tone. At elevated levels of vasomotor tone the resistance decrement to tetraethylammonium is larger than that decrement observed at low levels of tone. When tetraethylammonium was administered to hypertensive and to normotensive subjects the relative decreases in peripheral resistance were the same in both groups, suggesting that the prevailing level of neurogenic vasomotor tone in the extremities is not increased in hypertension.

Acknowledgment

We gratefully acknowledge the assistance of Dr. William E. Reynolds of the Department of Preventive Medicine, Harvard Medical School for his evaluation of the data.

Sumario Español

Tetraetiloamonio (TEA) administrado intravenosamente disminuye la resistencia periferal vascular. La magnitud del decremento se relaciona directamente al nivel prevalente del tono vasomotor neurogénico. TEA fue administrado a sujetos normotensos e hipertensos. Los decrementos en resistencia del pié no difirieron entre los dos grupos. Los decrementos del antebrazo tampoco difirieron. Estos hallazgos sugieren que el nivel prevalente de tono vasomotor neurogénico en las extremidades no esta aumentado en hipertensión.

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The Effect of Priscoline on the Clearance of Radiosodium from Muscle and Skin of Man in Normal and Diseased Limbs

By JACK FREUND, M.D., LAWRENCE H. WISHAM, M.D., AND ROSALYN S. YALOW, PH.D.

The radiosodium clearance technic was used to measure the effect of Priscoline given intra-arterially on the effective blood flow in muscle and skin of normal subjects and patients with peripheral vascular disease. The only clinically significant increase in the clearance rate of radiosodium (Na^{24}) occurred in the skin; the clearance rate in muscle showed small increases which were constantly present but not considered to be clinically significant.

THE RECENT work of Kety[1, 2] introduced a method of indirectly measuring the effective blood flow in human muscle by determining the rate of clearance of injected radiosodium (Na^{24}). Other investigators[3-6] have studied the clearance of radiosodium from the gastrocnemius muscle in normal subjects and patients with peripheral vascular disease. They concluded that the method was an additional tool in evaluating the circulatory physiology of an extremity and suggested its use in evaluating therapy.

The authors[7] have previously demonstrated that the clearance rates of radiosodium from the gastrocnemius and biceps muscles in normal man were reproducible in the same individual within a significant predictable range over a period of three months.

The present study was undertaken to observe the effect of Priscoline on the clearance of radiosodium from the calf muscle and overlying skin of patients with arteriosclerosis obliterans, and individuals with normal cardiovascular systems.

MATERIALS AND METHODS

The subjects for this study consisted of two groups of male patients. In the first group were patients from the Cardiovascular Section of the Medical Service with symptoms and objective findings of peripheral vascular disease. During their hospital stay, these patients were also evaluated in the peripheral vascular disease clinic where Landis-Gibbon tests[8] and posterior tibial blocks were performed. The pertinent history, physical findings, and laboratory data are summarized in table 1. The subjects in the second group were male patients between the ages of 20 and 40 with normal cardiovascular systems. There were 74 studies on 14 patients with peripheral vascular disease, and 15 studies on six normal subjects. Prior to each experiment, the subject rested in the laboratory in the supine position for 10 minutes. The temperature of the laboratory was maintained between 75 and 78 F.

An isotonic solution of sodium chloride containing 3 to 5 microcuries of radiosodium per 0.1 cc. of solution was used in all experiments.

In the studies on muscle, 0.1 cc. of radiosodium solution was injected into the belly of the gastrocnemius muscle using a 20 gage, one and one-half inch needle inserted to the hilt. The skin injections were made with a 26 gage needle, raising a bleb in the skin over the calf with .03 to .05 cc. of radiosodium solution. In all the patients with arteriosclerosis obliterans except Mas, the skin and muscle studies were performed on the same limb. Immediately after all injections of radiosodium, a thin mica-window Geiger counter was placed in a fixed position[9] at a 45 to 90 degree angle to the long axis of injection and counting was started. The activity was recorded, using a scaling circuit with scale selections at 16, 32, 64 and 128. An automatic printer recorded register readings at intervals of one minute for one hour during muscle determinations. Raw data at two-minute intervals were plotted on semilogarithmic paper.

In the experiments on skin, the Geiger counter was placed directly over the injection site. All subjects were advised against moving the limb being studied.

From the Medical Service and Radioisotope Unit, Veterans Administration Hospital, Bronx, N. Y.

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TABLE 1.—*Clinical and Laboratory Findings*

Name	Age	Limb	History	Physical	Oscillometrics		Post-Tibial Blocks	Landis-Gibbon	Diagnosis
					Below knee	Above ankle			
Bat	57	Rt.	Diabetes 12 yrs.; intermittent claudication and burning feet 2 to 3 yrs.	Femoral pulses good; popliteal pulses questionable; foot pulses absent	Rt. ½ Lt. ½	0 0	Negative for temperature rise	Negative for temperature rise	Arteriosclerotic heart disease; arteriosclerosis obliterans; diabetes mellitus
Sho	62	Lt.	Diabetes 20 yrs.; ulcer plantar arch rt. foot 2 to 3 mos. with pain and swelling rt. foot	Atrophic changes in nails bilaterally; patent femorals and lt. popliteal; other pulses absent	Rt. 1 Lt. 6	0 0	Negative for temperature rise	Negative for temperature rise	Diabetes mellitus; arteriosclerosis obliterans; ulcer rt. foot
McC	63	Lt.	Dyspnea on exertion 2 mos.; intermittent claudication (bilateral) 2 to 3 mos.	Both femoral and rt. popliteal pulses present; other pulses absent	Rt. 7 Lt. 0	1½ 0		Maximal dilatation prior to procedure	Arteriosclerotic heart disease; arteriosclerosis obliterans; pulmonary emphysema
Alb	71	Rt.	Intermittent claudication (bilateral) 8 yrs.; burning rt. foot 1½ yrs.	No pulses below femorals; rt. foot mottled cyanosis	Rt. 0 Lt. Flicker	0 0	No significant rise in temperature		Arteriosclerosis obliterans
Fin	63	Rt.	Mummification of 2nd and 4th rt. toes without premonitory signs 4 mos.	Both femorals and popliteals present; all foot pulses absent	Rt. 6 Lt. 3	trace trace	Negative for temperature rise		Arteriosclerosis obliterans
Bri	64	Lt.	Intermittent claudication 6 yrs.	Pallor of toes; lt. foot pulses absent; rt. post-tibial present; popliteals and femorals normal	Rt. 6 Lt. 4	2 0			Cor. pulmonale; arteriosclerosis obliterans

Bic	51	Lt.	Intermittent claudication 4 yrs.	Only femorals patent BP 210/110	Rt. ½ Lt. 1½	¼ ¼			Hypertensive and arteriosclerotic heart disease; arteriosclerosis obliterans
Kle	60	Rt.	Above knee amputation for acute arterial occlusion lt. lower extremity 1947; cardiac decompensation 1948	Rt. femoral and popliteal good; only post-tibial felt; lt. femoral absent; rt. foot cold and cyanotic	Rt. 10 Lt. 0	1 stump	7 degree temperature rise in toes	6 to 7 degree rise in toes of foot	Arteriosclerotic heart disease; arteriosclerosis obliterans
Gre	56	Rt.	Diabetes 10 yrs.; 2 episodes of myocardial infarction; intermittent claudication (bilat.) 3 yrs.	Absent arterial pulses below femoral	Rt. 5 Lt. 2	2 ½	8 degree rise in temperature of toes rt. foot	4 to 5 degree temperature rise both feet; results equivocal	Arteriosclerotic heart disease; diabetes mellitus; arteriosclerosis obliterans
Hel	39	Lt.	Gangrene lt. toe of 2 mos. duration	Absent lt. post-tibial and lt. dorsalis pedis; mummification lt. great toe	Rt. 9 Lt. 8	5 4–5	Good response on rt.; limited on lt. 4 degrees	Equivocal response on lt.	Thromboangiitis obliterans
Nev	37	Rt.	Frost bite 1942 with cold sensitivity since; persistent cyanosis ending in gangrene great rt. toe 7 wks. duration	No dorsalis pedis and faint post tibial on rt., both feet cold, rt. foot sweating profusely	Rt. 8 Lt. 9	2½ 3	Excessive sweating completely disappeared after injection. No rise in temperature	Equivocal response	Thromboangiitis obliterans with prior cold-sensitization and frost bite

Prior to the intra-arterial injections, the skin and subcutaneous tissue over the femoral artery of the ipsilateral limb were infiltrated with 1 to 2 cc. of 1 per cent procaine. Priscoline, 37.5 mg., was then injected into the femoral artery over a period of 30 seconds. Following removal of the needle, the site was compressed for 30 to 60 seconds to prevent hematoma formation. Similar pressure on non-injected subjects did not result in an increase in

75 mg. in 500 cc. of 5 per cent glucose in sterile water, was infused into the femoral artery over a period of one hour. The radiosodium was injected into the muscle two to three minutes after the infusion was started.

The time between studies on any one individual varied from one day to four months.

In all experiments the data were plotted on semi-logarithmic graph paper as a function of time. A

TABLE 2.—*Radiosodium Clearance from Gastrocnemius Muscle in Arterial Vascular Disease*

		Clearance Constant (Minutes^{-1})				Clearance Half Life (Minutes)			
Name	Age	Values	Average K Constant	Intra-arterial Priscoline	Average	Controls	Average Half Life	Intra-arterial Priscoline	Average
Bat	57	.092	.093	.079	.078	7.50	7.41	8.75	8.85
		.099		.078		7.00	9.00		
		.089				7.75			
Sho	62	.066	.066	.073	.081	10.50	10.50	9.50	8.52
		.066		.089		10.50		7.75	
McC	66	.060	.071	.073	.071	11.50	9.75	9.50	9.75
		.082		.069		8.50		10.00	
Alb	71	.082	.075	.058	.059	8.50	9.27	12.00	11.70
		.068		.060		10.25		11.50	
Fin	63	.851	.072	.073	.085	13.50	9.61	9.50	8.20
		.066		.099		10.50		7.00	
		.099		.082		7.00		8.50	
Bris	64	.068	.068	.099	.099	10.25	10.25	7.00	7.00
Blo	51	.096	.082	.087	.087	7.25	8.48	8.00	8.00
		.068				10.25			
Kle	60	.066	.070	.089	.095	10.50	9.84	7.75	7.28
		.079		.089		8.75		7.75	
		.066		.106		10.50		6.50	
Gre	56	.079	.075	.060	.060	8.75	9.24	11.50	11.50
		.064		.060		10.75			
		.082				8.50			
Goe	41	.069	.078	.099	.096	10.00	8.90	7.00	7.25
		.087		.092		8.00		7.50	
Gut	43	.069	.075	.099	.099	10.00	9.18	7.00	7.00
		.082				8.50			
Tho	51	.069	.074	.102	.102	10.00	9.35	6.76	6.76
		.079				8.75			
Hel*	39	.115	.115	.163	.138	6.00	6.00	4.25	5.02
				.111				6.25	
Nev*	42	.115	.115	.111	.111	6.00	6.00	6.25	6.25

* Patients with Thromboangiitis Obliterans

the clearance constant. The injection of Priscoline was not considered intra-arterial unless the following were present; a pulsatile red column seen in the syringe, obvious and intense flushing of the skin, evidence of a pilomotor response of the skin of the limb, and the sensation of heat extending down the extremity. The radiosodium injection was made two to three minutes after completion of the intra-arterial injection.

The apparatus described by Mufson[10] was used for the intra-arterial infusion of Priscoline. Priscoline,

previously demonstrated,[7, 9] a curve consisting of two components was obtained when radiosodium clearance from muscle was observed for one hour. Background activity, due largely to sodium deposited in subcutaneous tissue, was derived from a straight line drawn through the last 8 to 10 plotted points on the curve and extrapolated back. This background activity was then serially subtracted from the raw data. The clearance from muscle was finally calculated from the slope of the straight line obtained by plotting the net activity.

In the studies on radiosodium clearance from skin, a straight line slope was obtained from a semi-logarithmic plot of the raw data.

The time taken for the activity present initially to be decreased to one-half is the clearance half life. The clearance constant (K) is equal to the natural logarithm of two divided by the clearance half life; thus $K = \frac{0.693}{T_{\frac{1}{2}}}$.

Results

The results for each experiment are expressed both in terms of clearance half life and clearance constant.

There were 49 studies of the clearance of radiosodium from the gastrocnemius muscle in 12 patients with arteriosclerosis obliterans; of these 27 were controls; the remaining 22 were studies of clearance from muscle of a rapid injection of 37.5 mg. of Priscoline into the femoral artery. The average clearance constant for the 12 patients with arteriosclerosis obliterans was 0.075 minute^{-1}. The average clearance constant for these same 12 patients following the injection of Priscoline intra-arterially was 0.083 minute^{-1}. These results are shown in table 2.

In two patients with thromboangiitis obliterans, the rapid injection of Priscoline into the femoral artery did not produce any significant change in the clearance of radiosodium from the gastrocnemius muscle when compared with control studies (table 2).

There was no difference observed in the clearance during an intra-arterial Priscoline infusion as compared with the rapid injection of Priscoline in three subjects.

Table 3 gives the results of 15 observations on the clearance of radiosodium from the gastrocnemius muscle in six individuals with normal cardiovascular systems. Six of these studies were performed immediately following the rapid intra-arterial injection of 37.5 mg. of Priscoline, and nine were control studies.

TABLE 3.—*Radiosodium Clearance from the Gastrocnemius Muscle in Normal Subjects*

	Clearance Constant (Minutes^{-1})			Clearance Half Life (Minutes)		
Name	Controls	Average K	I. A. Priscol	Control	Average	I. A. Priscol
Bar	.126	.115	.120	5.50	6.02	5.75
	.087			8.00		
	.132			5.25		
New	.138	.138	.163	5.00	5.00	4.25
Pur	.099	.099	.126	7.00	7.00	5.50
Vel	.103	.103	.126	6.75	6.75	5.50
Sch	.120	.120	.115	5.75	5.75	6.00
Ter	.115	.100	.103	6.00	6.95	6.75
	.084			8.25		

TABLE 4.—*Skin Clearance in Arteriosclerotics*

	Clearance Constant				Clearance Half Life			
Name	Control Minutes^{-1}	Average	I. A. Priscol Minutes^{-1}	Average	Control Minutes	Average	I. A. Priscol Minutes	Average
Bat	.029	.029	.044	.042	24.25	24.13	16.00	16.60
	.029		.037		24.00		18.50	
			.044				15.75	
Sho	.018	.018	.040	.040	38.50	38.50	17.50	17.50
Mas	.053	.053	.103	.103	13.00	13.00	6.75	6.75
Fin	.029	.029	.041	.041	24.00	24.00	17.00	17.00
Bre	.049	.048	.069	.069	14.00	14.50	10.00	10.00
	.046		.048*		15.00		14.50 (IV)*	

* Priscoline injected intravenously

The average clearance constant for the six subjects studied was 0.113 minute^{-1}, while the average clearance constant following injection of Priscoline was 0.126 minute^{-1}.

Table 4 gives the results of 14 observations on the clearance of radiosodium from the skin over the calf of five patients with arteriosclerosis obliterans. There were seven control studies and seven studies immediately after the rapid injection of 37.5 mg. of Priscoline

into the femoral artery of the same limb. The average clearance from the skin in these subjects was 0.035 minute^{-1}, while in these same subjects the average clearance constant following the injection of Priscoline was 0.059 minute^{-1}, an increase of 69 per cent in the average clearance constants. In all patients studied, there was a marked increase in clearance of radiosodium from skin after the intra-arterial injection of Priscoline. This increase ranged from 42 to 119 per cent. In one patient, G. H., in whom Priscoline was inadvertently injected into the femoral vein, no increase in clearance from the skin was noted.

Discussion

A vasodilator drug given orally or intravenously will result in a generalized vasodilation which will not give an increased flow of blood to a local area, assuming no change in cardiac output. In arterial peripheral vascular disease there is organic narrowing of the lumen of involved vessels. Such vessels will offer greater resistance to the dilatation effect of drugs than the uninvolved vessels of the body. Therefore, any drug producing a generalized vasodilatation would be an ineffective method of producing an increased blood flow in diseased peripheral vessels. In order to get a localized vasodilatation and to minimize any possible effect on cardiac output in our studies, the drug was given by injection into the femoral artery.

Priscoline (benzylimidazoline), now widely used as a vasodilator in peripheral vascular disease, was the drug selected for study. The complex pharmacodynamic relationships in animals caused by this drug have been described by Ahlquist and co-workers.[11] They observed peripheral vasodilatation, cardiac stimulation, coronary vasodilatation and an increased cardiac output. However, Grimson[13] found no significant changes in cardiac output following the intravenous injection of Priscoline, as determined by cardiac catheterization and variable results, using the ballistocardiograph. Chess and Yonkman[14] studied the effect of Priscoline in animals and stressed the varying sympatholytic and adrenolytic properties of the drug.

It is evident from the clinical chart (table 1) that all the subjects not considered normal in this study had definite occlusive peripheral vascular disease with findings of absent pulses and decreased to absent oscillometric readings in the involved areas. In only two of the 12 patients with arteriosclerosis obliterans was there evidence of vasospasm suggested by a good response to either posterior tibial block or the Landis-Gibbon test.

In normal subjects the average response to intra-arterial injection of Priscoline was small (7 per cent). The average control clearance constant was 0.113 $\pm$ 0.012 minutes^{-1} compared with the average (K) following Priscoline injection of 0.126 $\pm$ 0.015 minutes^{-1}.* The effect of Priscoline is small but statistically significant.

If the same statistical analysis is applied to the results for patients with arteriosclerosis obliterans, the increase following Priscoline is 15 per cent and the range for the average clearance constant of the control studies will be 0.075 $\pm$ 0.004 minutes^{-1}. The average K for these patients following Priscoline injection was 0.083 $\pm$ 0.008 minutes^{-1}, again indicating that the effect in muscle was statistically significant although too small to be clinically important.

In the skin of the patients with arteriosclerosis obliterans, the response to Priscoline was much more marked. There is an average increase of 69 per cent if the means for the control clearance constant and the clearance constant following Priscoline injection are compared. The increases varied in each individual from 42 to 119 per cent. If the same statistical analysis as above is applied here the range for controls will be 0.036 $\pm$ 0.012 minutes^{-1}, while the mean clearance constant following Priscoline is 0.0588 $\pm$ 0.0218, showing a much greater response of the blood vessels in the skin than the blood vessels in the muscle.

In two of our subjects who had evidence of vasospasm and in two patients with minimal

* The standard error is found from the formula:

$$\text{Standard Error} = \sqrt{\frac{(\text{Sum of Differences from mean})^2}{(\text{Number of studies})}}$$

occlusive changes the response to intra-arterial Priscoline was in no way strikingly different from the other patients in this group.

The average clearance constant of the 12 patients with arteriosclerosis obliterans in this study was 0.075 minutes^{-1}; the average clearance constant for the normals studied was 0.111 minutes^{-1}, and the average clearance for the patients with thromboangiitis obliterans was 0.116. If these figures are compared with the average clearance constant for the muscle of 101 normal subjects of 0.106 minutes^{-1}, as reported by Wisham and Yalow,[9] it becomes evident that the clearance rate in patients with arteriosclerosis obliterans is considerably slower than in normals, as expected, that in the present series the mean clearance constant in the normal subjects agrees very closely with that previously obtained (slightly more than a 5 per cent difference), and that the clearance constants for patients with early thromboangiitis obliterans are very similar to those of normals.

Cooper and co-workers[5] noted a more rapid clearance of radiosodium from the gastrocnemius muscle in patients in the early stages of thromboangiitis obliterans than in normal patients. We have noted a similar tendency in the two cases herein reported and in two additional unpublished cases. However this increased rate of clearance is small and is not statistically significant.

An extensive study of peripheral blood flow by various methods was reported by Cooper and Elkin.[6] One method was the local clearance of radiosodium from the muscle. They reported that the clearance rate of radiosodium from the muscle was slowed when Priscoline was given intravenously. They concluded that the increase in blood flow to the skin caused a diversion of blood from muscle, thus resulting in a smaller blood flow to muscle. This disagrees with our finding of a small increase in the muscle clearance rate. In their study the clearance rate was determined for 10 minutes as a control and then Priscoline was given intravenously, as compared with the intra-arterial injection in our experiments, and the clearance rate again determined. It has previously been observed that a considerable amount of the injected radiosodium is cleared shortly after injection into a muscle and that some of the radiosodium is deposited in subcutaneous tissue.[7, 9] The recorded activity from subcutaneous tissue, where the clearance rate is considerably slower, then becomes a significant factor. This may well account for the discrepancy between their results and ours.

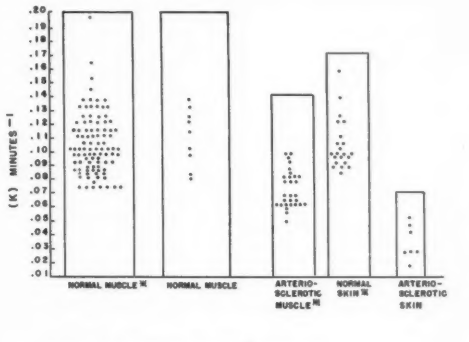

FIG. 1. A scattergram showing the clearance constants in normal and pathologic muscle and skin.

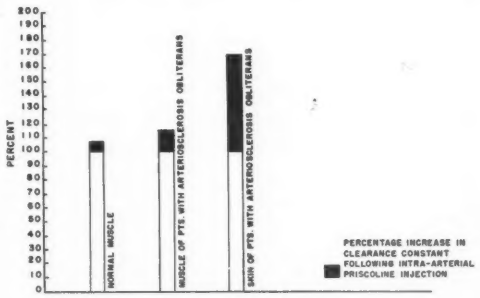

FIG. 2. A comparison of the response to rapid intra-arterial injection of Priscoline in normal and arteriosclerotic muscle and skin.

However our conclusions are in agreement: the major vasodilator effect of Priscoline is on the skin.

Murphy and associates[12] studied the effect of Priscoline given intravenously on peripheral blood, using both the venous occlusion plethysmograph and the radiosodium clearance methods. They reported an average increase of 59 per cent in blood flow as determined by the plethysmograph and a decrease of 36 per cent

in muscle blood flow with the clearance technic. These investigators used the method described by Cooper and Elkin,[6] which has been discussed above. They suggested that the decrease in muscle blood flow was probably a result of the increased blood flow in the skin. That such a mechanism does not take place is indicated by our finding of a small increase in muscle blood flow; although we agree with these investigators that the major effect of Priscoline is on the blood vessels of the skin.

The increase in over-all blood flow of 59 per cent following injection of Priscoline intravenously is not inconsistent with our findings of an average increase of 69 per cent in skin and an average increase of 11 per cent in muscle following injection of Priscoline intra-arterially.

The authors feel that the radiosodium clearance method is a valuable tool in obtaining information on the effect of a therapeutic agent on the various tissues of an extremity in health and disease. Since the effect of Priscoline on local muscle flow is small and far less than the effect of moderate exercise,[7] the value of this drug in relieving intermittent claudication in patients with organic occlusion is questionable. Its suggested use for maintaining the integrity of the skin in peripheral vascular disease appears to have some justification when the drug is administered intra-arterially.

Summary

1. The effect of Priscoline administered by rapid injection intra-arterially on the clearance of radiosodium from the gastrocnemius muscle and overlying skin was studied in patients with peripheral vascular disease and in normal subjects.

2. In 59 studies on 12 patients with arteriosclerosis obliterans and two patients with thromboangiitis obliterans, and 15 studies on six normal subjects, Priscoline caused a small but not clinically important increase in the clearance rate of radiosodium from gastrocnemius muscle.

3. There was a significant increase (average of 69 per cent) in radiosodium clearance from the skin overlying the calf muscle in 14 experiments on five patients with arteriosclerosis following the intra-arterial injection of Priscoline.

4. The possible clinical implications of these observations have been discussed.

Sumario Espanol

El efecto de la Priscolina administrada intrarterialmente en la circulación sanguínea efectiva del músculo y la piel en sujetos normales y pacientes perífero vasculares se determinó mediante la técnica de la eliminación del radiosodio. El único incremento de significado clínico en el promedio de eliminación de Na^{24} ocurrió en la piel; el promedio de eliminación en el músculo mostró solamente ligeros incrementos que fueron constantes pero no considerados como clínicamente significantes.

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The Effect of the Frequency Response of Electrocardiographs on the Form of Electrocardiograms and Vectorcardiograms

By A. J. KERWIN, M.D., M.R.C.P. (LONDON), F.R.C.P. (CANADA)

The spectrum of frequencies making up the cardiac potential has not been fully explored. Limitation in the high frequency response of most electrocardiographs suppresses in some tracings QRS components whose significance is at present obscure. Using the cathode ray oscillograph it was found that frequencies as high as 1300 cycles per second reveal characteristics not shown at lower frequencies. Frequencies as high as 6400 cycles per second are under investigation. Limitation of the low frequency response by the use of a condenser-resistor network to abolish extraneous potentials produces serious distortions of the RS-T segment.

SCANT ATTENTION has been paid to the effect of the capabilities of the recording equipment on the form of the electrocardiogram. Until recently the inherent limitations of most electrocardiographs, particularly with respect to frequency response, have been such that investigation of this problem was not easy. Moreover, with the best available apparatus, records seemed to be satisfactory and indeed often showed (and still do show) characteristics beyond the limits of our ability to interpret them.

For two reasons interest in this problem has recently been stimulated. The first is the introduction of the direct writing instruments. Some of the records, particularly of the early models, showed "smoothing" out of the curves and low amplitudes, attributable to limitation of high frequency response. In order to accept the direct writer as a satisfactory recording instrument, it is necessary to show that even with its limited range, all or nearly all of the components of physiologic or pathologic significance are detected. This is indeed a formidable task and even if it proved to be so in the present state of our knowledge, future progress in some directions might be hampered by the widespread use of such instruments in research.

The second reason for our interest is that the development and improvement of cathode ray apparatus has enabled us to investigate a much wider band of frequencies than was heretofore feasible. It should thus eventually be possible to determine (1) whether the present instruments are satisfactory for routine clinical use, and (2) whether a greatly increased frequency range is of value in research. There are of course other recording characteristics capable of improvement, but our attention will be directed only to the frequency response. No attempt has been made to study the problem of phase shift.

In late years, there has been almost no interest in the low frequency characteristics of electrocardiographs. The advent of the amplifier type of recorder some years ago raised the problem of the amount of distortion of slow waves introduced by the time constant factor. It was finally agreed that a time constant of 2.0 seconds or more would give almost distortionless reproduction of slow components and this standard is achieved by practically all commercial instruments. Recently an attempt has been made to minimize low frequency potentials from sources outside the heart by decreasing the time constant. Certain of the tracings thus recorded showed characteristics which appeared to be caused by too short a time constant. It

From the Department of Medicine, The Toronto Western Hospital and the University of Toronto.

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was thought advisable to re-investigate this problem.

High Frequency Response

Little work has been done to determine the relative magnitudes of the various harmonics of the cardiac potential. Einthoven was certainly aware of the problem because he succeeded in reaching a frequency response of 300,000 cycles per second by the use of a fine string less than 1 mm. in length.[1] In 1912 he wrote,[2] "If the string reaches its new position of equilibrium within about 0.01 second or less, the instrument is rapid and at the same time sensitive enough for recording E.K.G. s with sufficient accuracy. The deviations from an ideal E.K.G. which a curve recorded under these conditions exhibits are so small that in the great majority of cases they may be neglected. . . . We are now justified in making the following conclusion. If the movements of the string could be made 10 to 100 times faster, the sensitiveness remaining the same, or even if, theoretically spoken, an instrument were available with an infinitely small deflection time, the form and dimensions of the recorded E.K.G. s would not be thereby perceptibly changed."

Einthoven's conclusions appear to have been generally accepted without much question. Wiggers[1] in 1929 seems to have suggested that a frequency response of about 20 cycles per second was sufficient for practical purposes. In 1933 Reid and Caldwell[3] re-investigated this problem using an oscillograph and amplifier having a much higher frequency response than the string galvanometer. Harmonic analysis indicated that the more rapid frequency components had significant magnitude and that the one hundredth harmonic was twice as large as the fundamental.

In May 1947 the Council on Physical Medicine[4] of the American Medical Association laid down minimum requirements for electrocardiographs and specified that the amplitude response to a 1 mv. alternating (or sinusoidal) signal must be not less than 50 per cent at 40 cycles. In June 1950 this was revised[5] so that the response ". . . up to 40 cycles per second shall not fall below 80 per cent of the square wave response to equivalent voltage variation." This specification is low enough to make acceptable most of the popular makes of instruments. Some of the early models of direct writers barely reached this level of performance; the later ones are better, but it is evident that the inertia of the writing apparatus is a limiting factor which will never permit it to approach the frequency capabilities of the cathode ray oscillograph.

The problem remained in abeyance until it was taken up by Gilford of the United States Bureau of Standards. Preliminary results[6] were reported in 1948 and his tentative conclusions may be reasonably summarized as follows: (1) The necessary frequency response characteristics of electrocardiographs have not yet been accurately specified, but probably should be flat to 200 cycles per second, a figure not attained by most available instruments. (2) Research demands instruments with a wider frequency range than heretofore used. An interim report[7] of further work was made in 1949. Simultaneous tracings were made with several standard models and compared with that of a wide-band cathode ray recorder whose response was down 3 decibels at 1200 cycles. As we shall see, this is somewhat better than we had arbitrarily selected as our highest response. Gilford felt that the direct-writer was adequate for routine purposes but that research required high fidelity apparatus with a frequency response up to 200 cycles.

It has been customary to make instruments only slightly better than good enough to meet the presumed requirements, partly because of cost and partly because operating complications are introduced at higher frequencies. It is obvious that previous assumptions about frequency response requirements are not based on exact information and that further investigation is indicated.

Method

The ability of the recording instrument to respond to signals of different frequencies may be tested by putting in a sinusoidal signal of constant voltage and measuring the amplitude of the recorded deflections at each selected frequency. When

the frequency of the signal is increased a gradual and then a more abrupt decrease in the magnitude of the response takes place as the limit of the instrument is reached. (See fig. 1.)

It was pointed out above that determination of the necessary frequency response characteristics of an instrument can be achieved by the harmonic analysis of records taken with very high frequency apparatus and by estimating the relative amplitudes of the various harmonics of the complex action current. An adequate frequency limit may then be set at a point just above where the amplitude of

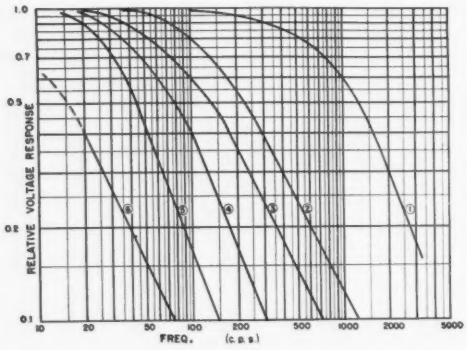

FIG. 1. Frequency response curves (logarithmic) showing the tap positions on the cathode ray electrocardiograph selected to represent approximately these conditions: (1) better than conventional electrocardiograph*; (2) commercially available cathode ray electrocardiograph; (3) typical string galvanometer; (4) direct writer; (5) minimum requirement of American Medical Association; (6) much below minimum requirement of American Medical Association.

the fast components is found to be too small to affect the shape of the curve visibly. This method is time-consuming and requires special apparatus and considerable mathematical skill. For these reasons, in this investigation we used the more practical method of taking records with different frequency response limitations and comparing them with one another in respect to amplitude and form. A definite change at a given level of response was taken to indicate suppression of more rapid components.

The cathode ray electrocardiograph used in these experiments had its high frequency response adjustable by a tap switch to six different settings, identifiable on figure 1 by the numbers one to six, position one having the highest response. The different responses available were chosen to represent to a first approximation the following conditions:

Position 1. Considerably better than any conventional electrocardiograph.

Position 2. Commercially available cathode ray electrocardiograph.*

Position 3. Typical string galvanometer type electrocardiograph.

Position 4. Direct-writer electrocardiograph.

Position 5. Minimum requirement as stated by Council on Physical Medicine of American Medical Association.[4]

Position 6. Appreciably worse than position 5.

(The data for determining positions 3 and 4 were obtained from the paper by S. R. Gilford.[6])

It was, of course, not always possible to make the response curves of the cathode ray unit agree exactly with the curves for the other types of electrocardiographs, but in general the curves are reasonably representative. In particular, Gilford's curves for string galvanometers actually fall between

TABLE 1.—*Frequency Response Characteristics (in Cycles per Second) of Tap Positions of Cathode Ray Electrocardiograph (see Fig. 1)*

Position	Frequency for 90% response (1 db. down)	Frequency for 70% response (3 db. down)	Frequency for 50% response (6 db. down)
1	300	760	1300
2	-	135	230
3	[illegible]	74	140
4	27	47	78
5	20	31	43
6	—	—	15

positions 2 and 3 above. In most cases the response curves on the cathode ray unit do not fall off as steeply as the curves for the other types of electrocardiograph. Table 1 shows the actual frequencies in cycles per second at which certain specific responses were obtained.

A large number of records were taken on a variety of normal and abnormal individuals. No attempt was made to study a particular type of case but many examples of congenital heart disease were utilized because high frequency components were common in this group. From 6 to 12 complexes were recorded for each tap position. Where there was variation in the form and size from complex to complex, the patient was asked to hold his breath during the recording. If the variation was not thereby abolished, the record was discarded. It was considered that a frequency response greater than

* At that time the response of the cathode ray electrocardiograph was deliberately limited to diminish possible amplifier noise and muscle potential. Current models are slightly better than position 1. Muscle potentials are largely eliminated by placing the electrodes on the upper arm and amplifier noise has not proven to be a problem.

1300 cycles would probably not be useful due to limitations in the resolving power of the recording system at the standard speed of 25 mm. per second. This has also been pointed out by Gilford.[6] In more recent experiments a variety of faster speeds has been employed.

For purposes of direct comparison simultaneous records were taken on four different types of instrument, (a) a cathode ray electrocardiograph set at position 1, (b) a popular amplifier type of mirror galvanometer recorder, (c) a recent (1950) model of a direct writer, and (d) a string galvanometer. Since the first three have a high impedance they were connected to common patient electrodes while a separate set had to be used for the string galvanometer. With the latter a chest lead on the same site could not, of course, be taken at the same time as on the other recorders. Identification of simultaneous complexes was achieved by pressing the four standardization switches at the same time.

Since the above investigation was completed a new cathode-ray, four channel, biologic recorder has become available.* It is capable of taking four simultaneous electrocardiograms or two simultaneous vectorcardiograms. The high frequency response can be limited by means of filters which decrease the response at a rate of 6 decibels per octave. The maximum frequency available was 6400 cycles per second for 6 decibels down (50 per cent voltage response), and the other tap positions were one octave apart at frequencies of 3200, 1600, 800, 400, 200, 100, 50, 25 and 12.5 cycles per second. At each of the levels the voltage response was 50 per cent (down 6 decibels). The slopes of the frequency response curves are similar to those of positions 2 and 3 in figure 1. In the examples shown later, frequency levels of 50, 100, 200 and 6400 cycles were selected so as to represent to a rough approximation the earlier American Medical Association requirement,[4] the performance of a string galvanometer, the level suggested by Gilford[6] and finally the maximal presently available with this apparatus. It must be appreciated that an increase of frequency response invites difficulties in the way of tube noise and high frequency interference. These may be reduced to a great extent by careful selection of tubes and proper preparation and placing of the patient and instrument, but some allowance must be made for minor irregularities of the base line particularly at high gains.

Results

No attempt has been made to study systematically a large series and determine statistically at what level of frequency response the form of the electrocardiogram would show all the necessary harmonics. It is, however, clear that many routine electrocardiograms appear to be satisfactory in this respect at a level of 135 cycles per second (3 decibels down). Some others show little change even at 74 cycles per second (3 decibels down). Below this level practically all records are distinctly altered.

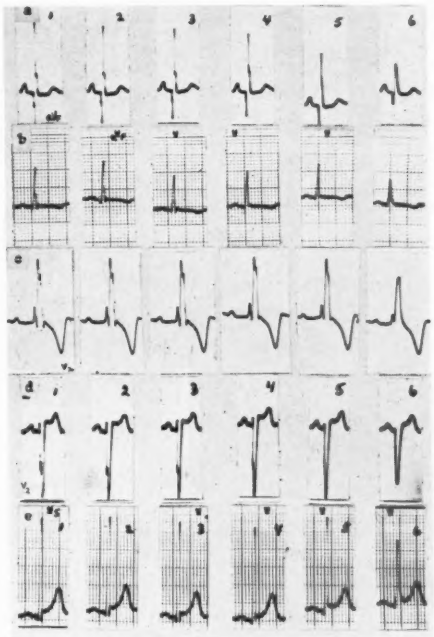

FIG. 2. Electrocardiograms of five different subjects (from above downwards) showing the tap positions numbered 1 to 6 as in figure 1, the highest frequency response being at the left and the poorest at the right. In this and in figure 3 time and horizontal lines have been removed from some of the records. Standardization 1 mv. = 1 cm.

These remarks apply of course only to tracings taken at standard speed.

The records seen in figure 2 were selected to show the type of changes encountered. The character of these changes is similar to those noted by Gilford,[7] namely, decreased amplitude, "smoothing out" of splintering and notching, and disappearance of small amplitude waves. In most of the waves measured only slight decrease in amplitude is noted at posi-

* Manufactured by Smith and Stone Ltd., Georgetown, Ontario, Canada.

tion 2, but becomes more marked as the frequency response is decreased. Apart from amplitude differences, inspection of the records shows progressive loss of beading and notching,

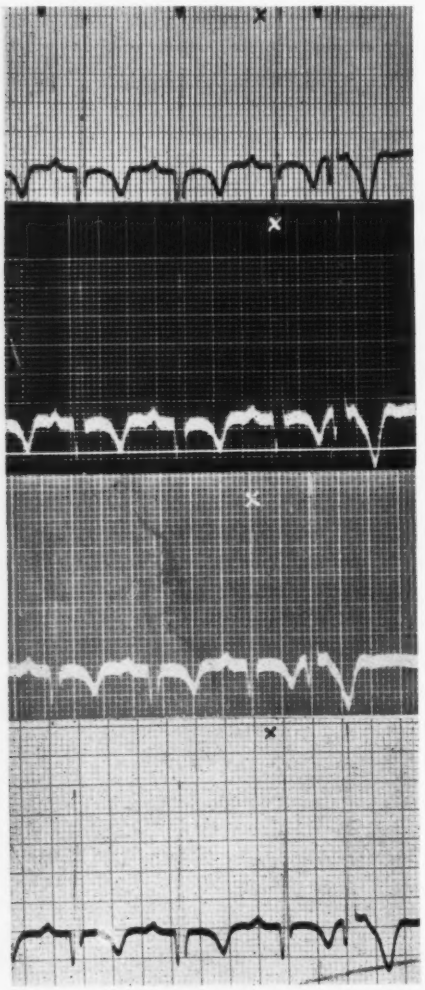

FIG. 3. Electrocardiogram taken simultaneously on four instruments: (from above downwards) cathode ray electrocardiograph, string galvanometer, mirror galvanometer, direct writer.

and increasing density and hence slowing of the trace from left to right. Since the electrocardiographic lead is but a scalar projection of the vector which is the resultant of a multitude of vectorial quantities, it is obvious that rapid reversals in the direction of the vector are visible on the electrocardiogram as notches which are minimized or wiped out in some types of apparatus with limited capabilities. In small animal records[8] very rapid waves form an important part of the complex, but whether they have any physiologic or pathologic significance in man is apparently unknown. It is our impression that young individuals with normal hearts are most likely to show these features. It would be interesting to know if there is a progressive loss of these fast waves in serial electrocardiograms in man over a period of years, particularly where the cardiac muscle is diseased.

In some cases progressive decrease and eventual obliteration of small amplitude waves were noted. In figure 2*c* this is well exemplified in the S and S′ waves. In figure 2*e* the Q is well preserved but the S decreases considerably at position 4 and disappears at position 5.

In figure 3 are shown simultaneous records on the four instruments, in order from above downwards, cathode ray, string galvanometer, amplifier and direct writer. In the complex denoted by *x* the S is clear in both cathode ray and direct writer records, present but small in the amplifier tracing and frequently absent in that of the string galvanometer. It is fair to assume that the cathode ray traces represent the maximum voltages obtainable with the frequency response at position 1. Overshooting of course cannot be a factor with a beam of electrons. The amplifier type revealed consistent defects of amplitude throughout. The direct writer showed up very well in the actual measurements and fairly well in the minor notchings too small to be calculated. It must be emphasized again that in a number of records the differences among the various recorders were of minor degree and not of significance in our present state of knowledge.

It cannot be denied that factors other than frequency response may have accounted in some degree for the variations in simultaneous complexes taken with different types of apparatus. Elimination of other possible factors was achieved by simultaneous recording of four

complexes on the same apparatus with the added and not inconsiderable advantage of increased paper speed to spread out and render more easily visible the rapid oscillations. In figures 4 and 5 are shown several series of such complexes at various recording speeds. In figure 4*a* and *b*, even at standard speeds, marked differences are quite evident. These are plainly seen between the records at 50 and 100 cycles and between 100 and 200 cycles but are not so obvious between 200 and 6400 cycles. Visibility is improved by increasing the paper speed to 100 mm. per second (fig. 4*c*) and is best at 250 mm. per second (fig. 4*d*). It should be noted that in fig. 4*c* only the P wave and QRS complex are shown and in fig. 4*d* only the QRS complex. The difficulties of labeling the various parts of the QRS complex are demonstrated in figure 4*c*. At frequencies of 50, 100 and 200 cycles, the main upward deflection would be called the R wave. But at a frequency of 6400 cycles the first downstroke returns to below the baseline and becomes an S wave and the process is immediately repeated. Hence, among other variables, the capabilities of the recording instrument influence the labeling of the complex.

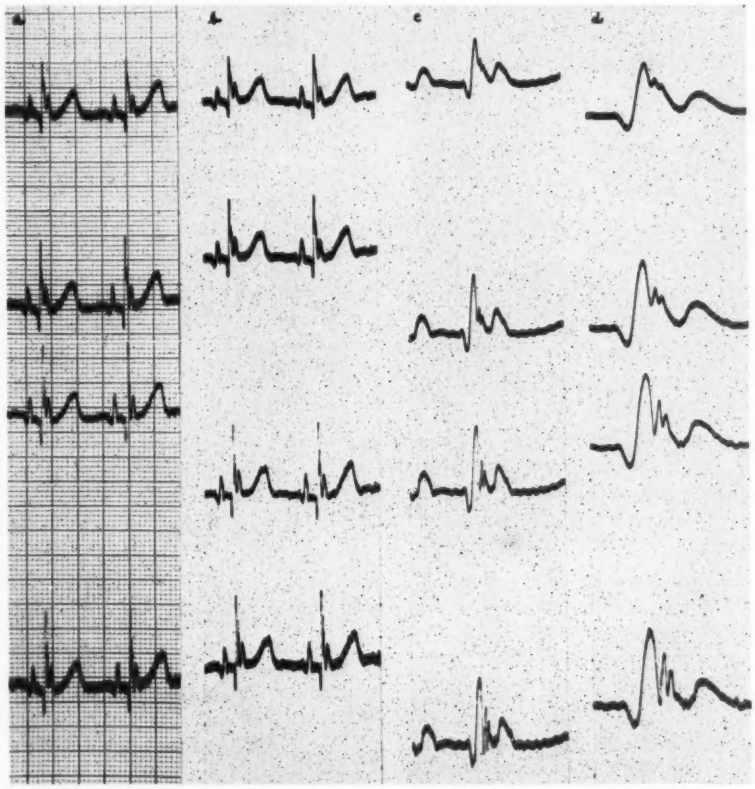

FIG. 4. Four simultaneous records of lead V_L of a normal subject taken at different frequency responses and different speeds. Top row 50 cycles per second, second row 100 cycles, third row 200 cycles, bottom row 6400 cycles (see text). Speeds: (*a*) 25 mm. per second, with time and height lines, (*b*) 25 mm. per second, without time or height lines, (*c*) 100 mm. per second, (*d*) 250 mm. per second. Standardization 1 mv. = 8.5 cm. (5N). In *c* only P and QRS are shown and in *d* only the QRS.

As previously noted, the amplitudes of the

components of a complex are greatly affected by restriction of the frequency response. Thickenings and slurrings of the trace become well defined notches at higher frequencies, especially when spread out (fig. 5*a* and 5*b*).

In figure 5*c* are shown the comparative deflection times of a standardization signal impressed on each channel at different frequency responses. At 6400 cycles the deflection time

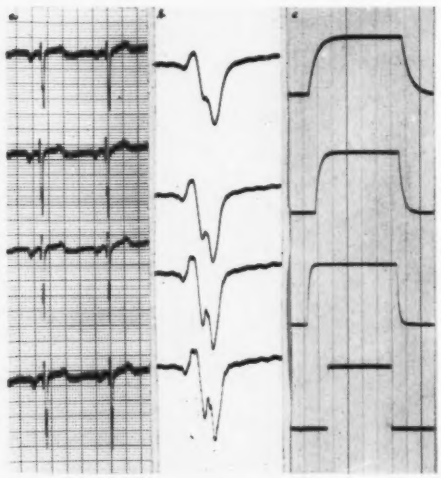

FIG. 5. Four simultaneous records of lead V_L taken at the following frequency responses (see text): top row 50 cycles per second, second row 100 cycles, third row 200 cycles, bottom row 6400 cycles. Speeds: (*a*) 25 mm. per second, (*b*) 250 mm. per second. Standardization 1 mv. = 8.5 cm. (5N). In *b* only QRS is shown. (*c*) Effect of frequency response on deflection time of standardization signal. Frequencies 50, 100, 200, 6400 cycles, from above downward. Speed 500 mm. per second. (The figure has been reduced to one-half original size.)

is practically zero, at 200 cycles it is about 0.002 second, at 100 cycles about 0.005 second and at 50 cycles, about 0.008 second.

Figure 6 demonstrates the effect of differences in frequency response on the form of the vectorcardiogram. In figure 6*a* the upper vectorcardiogram was taken at 6400 cycles and the lower simultaneously at 50 cycles. Considerable change in contour is evident. In figure 6*b* the upper vectorcardiogram was taken at 6400 and the lower at 200 cycles. Differences, though less marked, are still obvious. If any useful information is to be obtained from the vectorcardiogram other than the axis and the direction of the loop, high frequency apparatus should be utilized in the investigation.

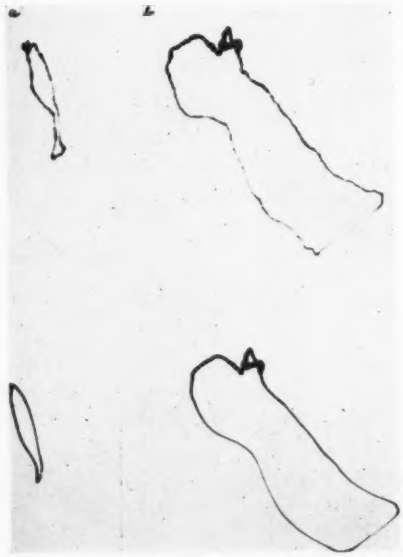

FIG. 6. Simultaneous frontal plane vectorcardiograms. (*a*) Upper, frequency 6400 cycles; lower 50 cycles. Standardization 1 mv. = 2 cm. (*b*) Upper, frequency 6400 cycles; lower 200 cycles. Standardization 1 mv. = 5 cm. (The figure has been reduced to one-half original size.)

LOW FREQUENCY RESPONSE

Low frequency components of the cardiac potential are accurately represented by the string galvanometer. The introduction into the field of electrocardiography of moving coil galvanometers requiring valve amplification aroused considerable controversy in the beginning as to the possibility of introducing distortions into the record. The property of a resistance-capacitance coupled amplifier usually termed "low frequency response" or "time constant" governs the amplifier's ability to reproduce faithfully a sustained departure of the wave form from the baseline. It is well recognized that if a steady direct current sig-

nal is applied to such an amplifier, the output will eventually return to the baseline,* following a curve which is usually logarithmic in shape. The time constant of an amplifier having such a decay curve is defined as the time required for the output response to fall to 36.8 per cent of its initial value when a steady direct current signal is applied.

Since the decay curve is logarithmic from the start Miller[9] modified the circuit so that decay did not begin for 0.1 to 0.2 second. The standard laid down by the Council on Physical Medicine[4] states that "the response of the instrument at 0.2 second after the application of a direct current of 1.0 millivolt shall not deviate more than ±10 per cent from the response at 0.04 second." If the shape of the decay curve is assumed to be truly logarithmic this corresponds to a time constant of approximately 2.0 seconds (see figure 7*e*). In this respect, most instruments in use today are presumably satisfactory.

Dock[10] found that capacitance in the circuit produced changes in the amplitude of S and T waves and displacement of the S-T segment. The distortions varied directly as the voltage of the QRS complex and inversely as the resistance and capacitance of the circuit. Ernstene and Levine[11] compared the records taken on 25 patients with both the amplifier type and the string galvanometer and found some decrease in amplitude with the former, but did not regard the difference as significant in most cases. Pardee[12] denied that the distortions found by Dock[10] could be due to capacitance. A detailed study of the effect of condensers in the patient-instrument circuit was made by Schwarzschild and Kissin.[13] They pointed out that "a capacitance represents an impedance to the flow of electric current inversely proportional to the frequency of alternation of the current. It offers a practically infinite impedance to low frequency currents which are evidenced by a drift ('skin current'), whereas it offers little impedance to currents caused by the rapidly fluctuating heart voltage." It was concluded that the important distortions introduced by the use of condensers lay in the amplitude of the R and deviation of the RS-T segment. They calculated that a time constant of 2.0 seconds would be sufficiently long to avoid most distortions and still permit reasonably rapid compensation for drift and similar effects. Recently this subject has been reviewed in detail by Lepeschkin.[14]

It is often difficult to obtain satisfactory esophageal leads because of extraneous low frequency potentials which cause considerable wandering of the base line. A condenser inserted in series with the patient will decrease low frequency potentials in the electrocardiogram.[14] Recently[15, 16] an attempt has been made to minimize these potentials by placing a condenser-resistor network having a time constant of approximately 0.1 second between the exploring electrode and the amplifier of the recording instrument. It was claimed that this attenuated frequencies of 1.5 cycles per second and less and had little effect on frequencies greater than 2.5 cycles per second. Records made with and without this filter were said to be similar. From the values for the condenser and resistor used, it is calculated

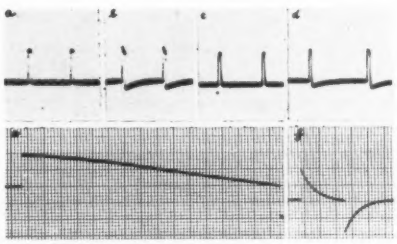

FIG. 7. (*a*) One millivolt signal with time constant of 2.0 second and high frequency response at position 1 (see fig. 1). (*b*) Same with time constant reduced to 0.1 second. (*c*) One millivolt signal with time constant of 2.0 second and high frequency response at position 4 (see fig. 1). (*d*) One millivolt signal with time constant of 0.1 second and high frequency response at position 4 (see fig. 1). (*e*) Decay curve with time constant of 2.0 second. (*f*) Decay curve with time constant of approximately 0.1 second.

* Strictly speaking, the level to which the waves decay is the "mean value" or the level having equal areas above and below it. With the wave forms of the type found in electrocardiography there is rarely any significant difference between the baseline and the mean value.

that the time constant of this network would be 0.1 second. Thus the output signal would fall to 36.8 per cent of its original value in only 0.1 second.

In the case of the steady direct current input signal previously mentioned, if the input is suddenly reduced to zero before the output has decayed completely to the base line, the output will be driven in the opposite direction by the full value of the original signal. If the duration of the signal is very short, the sloping top of the wave is often not obvious and only the overshooting below the base line is evident. However, the sloping top must actually be present if the overshooting is observed. The effects of high frequency and of low frequency response are interrelated insofar as the shape of the resultant record is concerned. If the high frequency response is limited, the upward deflection will be sufficiently slowed so that the downward slope at the summit will be minimized.

These distortions are demonstrated in figure 7. In figure 7*a* a 1.0 mv. standardizing signal of very short duration with a time constant of 2.0 seconds is shown. The top of the record is flat and the return to the base line is exact (see footnote on page 105). In figure 7*b* the time constant has been changed to 0.1 second and there is an obvious downward slope at the peak and a dip below the base line. Both of these records were made with the high frequency tap at position 1. (See fig. 1.) In figure 7*c* the high frequency has been reduced to position 4 (fig. 1) which slows the upstroke near the peak and the downstroke near the base line. In figure 7*d* both the low frequency and high frequency responses have been restricted. Compared with figure 7*b* the downward slope at the summit has been minimized while the base line depression has been little affected.

Although electrocardiographic wave forms are not composed of idealized square waves, one can make certain generalizations from what is known about the performance with square waves. Any interval in which the electrocardiographic wave is appreciably removed from the base line should be considerably shorter in duration than the time constant of the amplifier if the above type of distortion is to be avoided. The exact factor required obviously depends on how much distortion can be tolerated. On an idealized square wave a duration of time-constant/5 or longer would certainly produce noticeable distortion, whereas any duration less than approximately time-constant/20 would probably be accepted as free from distortion. Wave components very much shorter than the amplifier time constant (rapid, nearly vertical components) will be unaffected by the time constant and will be reproduced at their correct amplitude, provided of course that they are not so rapid that high frequency factors affect them.

The two most important types of wave in electrocardiography which are affected by a time constant as short as 0.1 second are the QRS and the T. In QRS complexes of average duration, say 0.08 second, some distortion may be expected since they are shorter than the amplifier time constant by a factor of less than 2. This will show up partly as a decrease in amplitude because during the rising interval the output will be decaying slightly, and even more noticeably as an overshooting of the base line at the completion of the QRS. Such components as T waves represent relatively long intervals of sustained deflection from the base line. Because these components do not even approach the time-constant/5 standard mentioned above for slightly noticeable distortion, one might expect to find severe distortion occurring with such waves. If the T were truly a square wave and of 0.3 second duration, distortion might be expected in an amplifier system having a time constant of 0.1 second. In the case of a component as long in duration as this example, even the American Medical Association requirement of a 2.0 second time constant might be considered as inadequate for completely distortionless amplification. Thus with the usual wave forms encountered in electrocardiography, the general effects of an inadequate time constant are premature return to the base line and overshooting.

Inspection of the records in the article by Scherlis and co-workers[15] suggested that some of the abnormalities were due to deficient low

frequency response. There are obvious advantages in such a circuit to facilitate the taking of esophageal electrocardiograms but it was felt necessary to investigate the possibility of having introduced distortions which would render the method valueless and indeed misleading.

Scherlis and associates[15] in their input circuit. Figure 7*f* shows the cathode ray amplifier output when a square wave is applied to the input. The time constant is seen to be very close to the 0.1 second value.

Figure 8 shows a series of complexes taken from a large number of patients, some of whom had cardiac infarction. The upper of each pair is the complex taken with the usual time constant while the lower is taken with the filter in the circuit, the resulting time constant being 0.1 second. Usually they were not recorded simultaneously but were taken on the same strip, the filter being inserted by turning a convenient control. In some cases simultaneous records were taken on two cathode ray electrocardiographs connected to the same electrodes, one having a "normal" low frequency response and the other a poor low frequency response.

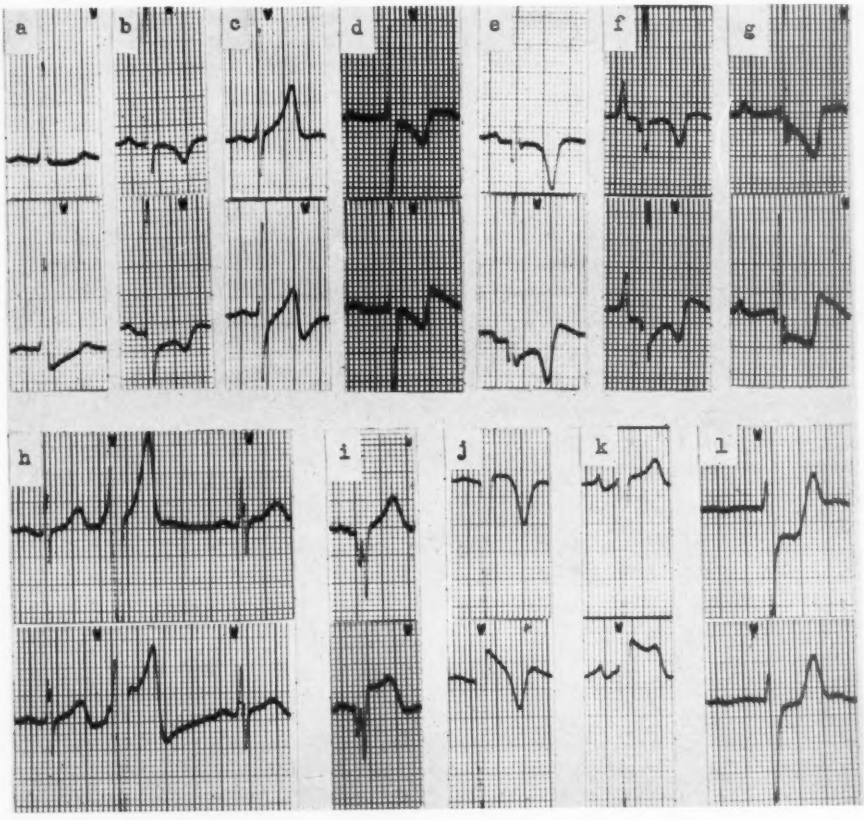

FIG. 8. Twelve pairs of complexes taken from a variety of normal and abnormal records. The upper of each pair has a time constant of 2.0 second and the lower a time constant of 0.1 second. In *a* and *b* the introduction of the filter has depressed the S-T segment and in *b* (only the premature beat), *i*, *j*, and *k* has elevated the S-T. In *l* the S-T depression caused by infarction has been almost completely abolished by the filter.

Method

To simulate the performance of an electrocardiographic system incorporating a filter of the type described, one of the coupling circuits in the cathode ray electrocardiographic amplifier was modified to give an over-all amplifier characteristic having a time constant of 0.1 second, the same as used by

Results

Depression of R-T or RS-T segment is well demonstrated in figure 8*a* and *b*. Elevation of S-T is seen in figure 8*h* (premature beat), *i*, *j* and *k*. Gross distortions of T wave are evident in figure 8*b*, *c* and *d*, and in figure 8*f*, *g*, *h* and *j*. While most of these deformities are of such a type as to simulate those associated with myocardial ischemia, the opposite change may be present. In figure 8*l*, the S-T depression caused by cardiac infarction is nearly abolished by the introduction of the filter.

Attention is drawn to figure 3 in the article by Scherlis and his colleagues.[15] The esophageal lead before exercise shows elevation of the S-T segment and an almost straight downward slope similar to that seen in our figure 8*k*. Leads E_8 and E_{10} in figure 2*a* of the paper by the same group[17] appear to show the same distortion. Esophageal lead E_3 in figure 1*a* of another report by the same authors[18] resembles our figure 8*l*. In another article[19] lead E_7 of figure 2 shows a resemblance to our figure 8*k*. Further examples of distortion can be found in the above mentioned tracings. Of course some leads will show little if any alteration, and in others changes due both to disease and to poor low frequency response will be present. It is possible to calculate the amount of this distortion[13] and to make allowance for it, but this seems an unnecessarily laborious procedure. With practice one can estimate visually the degree and kind of distortion introduced, but because the alterations in repolarization produced by ischemia of cardiac muscle have certain resemblances to those of defective low frequency response, the interpretation of such records is made difficult or misleading by the use of such a filter in the circuit.

Summary

The depolarization and repolarization of myocardial fibers results in changes in electrical potentials which take place both consecutively and simultaneously throughout the cardiac muscle. These potentials may be represented as vectorial quantities which at present cannot be isolated and analyzed individually, but which, added together, give a composite vector representing the resultant of all these forces regardless of the magnitude, sense and direction of the unit components. The electrocardiogram is the scalar projection of this vector on a chosen axis (lead). The potentials are made up of a variety of frequencies having different amplitudes at various times during the electrically active portion of the cardiac cycle. The origin and significance of the different frequencies of the currents are unknown and appear not to have been investigated. For several technical reasons, much of the recording apparatus has been incapable of registering the higher frequencies. Moreover, in the past, there has appeared to be no sound clinical or experimental reason for demanding instruments having an extended frequency spectrum. Recent changes and improvements in recording methods (direct writer and cathode ray electrocardiographs) have suggested the investigation of the changes in the form and amplitude of the electrocardiogram (and vectorcardiogram) which might be revealed by using high fidelity apparatus.

In some cases, except for slight loss of amplitude of QRS, little or no change could be found when a frequency above 47 cycles per second (3 decibels down) was used at normal paper speed and standardization. In others adequate representation was achieved with a frequency of 74 cycles while some tracings required at least 760 cycles. Although measurements of amplitudes of various parts of the QRS have a limited value in diagnosis, particularly in an individual case, any set of normal values should take into account the capabilities of the recording apparatus. In addition to changes in amplitude, with high frequencies slurring of QRS was altered to beading and notching caused by rapid changes in the direction of the vector in one or more planes which were suppressed at lower frequencies. Minor changes are obscured by the use of the conventional speed, which fact has recently been emphasized by Langner.[20]

The designation of different portions of the QRS by letters depends to some extent on the frequencies which are used (fig. 4*c*). Improvement in apparatus has permitted study

of frequencies as high as 6400 cycles per second, utilizing higher gains and speeds up to 500 mm. per second. Preliminary observations suggest that further investigation of this range is warranted. Langner[20] believes that a frequency response flat to 330 cycles per second or probably higher is needed for faithful reproduction of the electrocardiogram. Our results indicate that frequencies as high as 6400 cycles (6 decibels down) may be required for research purposes.

Low frequency components of the electrocardiogram are adequately represented with a time constant of 2.0 seconds. Although low frequency potentials arising outside the heart are minimized or abolished by reducing the time constant to 0.1 second, distortion of the wave form, particularly the RS-T segment, is frequently introduced, rendering accurate interpretation difficult or impossible. To some extent the effects of high and low frequency responses are interdependent so that restriction of the former minimizes the distortion of the latter (fig. 7).

Conclusions

1. The high frequency response of most commercially available electrocardiographs is so restricted that in some records distortion is produced by the suppression of rapid components of the cardiac potential.

2. The investigation of frequencies as high as 6400 cycles per second is warranted. These may prove to be of particular value in research.

3. No attempt has yet been made to assess the practical significance of high frequency components with respect to pathologic processes.

4. Satisfactory resolution of these changes requires an increase of recording speed up to as high as 250 or 500 mm. per second. At these speeds the use of several times the normal gain aids visualization.

5. The use of a condenser-resistor network to eliminate extraneous low frequency potentials which are particularly troublesome in esophageal leads is contraindicated because serious distortions of the RS-T segment may be introduced.

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Sumario Español

El espectro de frecuencias que constituyen el potencial cardíaco no se ha explorado detenidamente. Limitación en el respondimiento electrocardiográfico a altas frecuencias evita componentes Q.R.S. en algunos trazados cuyo significado permanece obscuro en el presente. Usando el oscilógrafo de rayo cátodo se encontró que frecuencias tan altas como 6400 ciclos están bajo estudio. La limitación al respondimiento a bajas frecuencias mediante el uso de un condensador-resistencia para abolir potenciales extraños produce deformaciones serias del segmento RS-T.

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CLINICAL PROGRESS

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The Heart in Anemia

By WILLIAM B. PORTER, M.D., AND G. WATSON JAMES, III, M.D.

THAT reduction in the oxygen carrying capacity of the blood has important effects on the normal as well as the diseased heart is not fully appreciated by many. This discussion will be concerned not only with the effect of anemia on the normal and the diseased heart but also with its effects on respiration and the metabolism of the tissues.

Many comprehensive discussions of the pathologic physiology of the cardiovascular and respiratory systems in anemia have appeared in current medical literature during the past years.[1, 2, 8] These are excellent sources of basic information for those interested in the complex problems of the physiologic adjustment to diminished oxygen-carrying capacity of the blood. In the present discussion, a less formal pattern will be adopted. At times statements will be made in the spirit of expressed personal opinion, obviously not based upon documented data. This is premeditated, for, convinced that many aspects of the total problem need additional study, we wish to be provocative.

Much of the obvious inconsistency in the great mass of published data stems from the failure of observers to be sufficiently critical of the type of patient selected for study. It is our conviction that any patient who has a varying degree of anemia, regardless of its duration, is not chronic from the standpoint of physiologic adjustment; acute stresses from a varying intensity of anemia introduce emergency reactions which do not operate in the fully acclimatized true "chronic anemia" seen in its most classic form in some parasitic anemias.

Four principle mechanisms may operate in anemia to maintain a normal or near normal oxygen supply to the tissues. These processes never function singly; the importance of each in a particular case depends upon the severity and the duration of the anemia. The four mechanisms are indicated by the following facts:

1. The cardiac minute volume output is increased.
2. The velocity of blood flow is increased.
3. The removal of a greater percentage of oxygen from each gram of circulating hemoglobin results in increased oxygen delivery to the tissues without burdening the heart.
4. Selective shunting of blood-to vital organs from areas of lesser importance is a process which operates in normal individuals but is developed more selectively and in greater magnitude during the stress of chronic anemia.

An increase in cardiac output in patients with anemia has been consistently demonstrated by most investigators, but the magnitude of the increase is not well correlated with either the degree or duration of anemia. The cardiac output is usually increased when the hemoglobin is 7 Gm per 100 cc. or less[3-8]; nevertheless, there are many exceptions. The predictable cardiac output in anemic patients is more consistently related to pulse rate and velocity flow than to the hemoglobin level.[8] This, however, is true only in anemias of varying degree or of short duration. When one investigates patients with parasitic anemia with relatively constant hemoglobin levels over periods of years, an increased cardiac output at rest is not indicated either by tachy-

From the Department of Medicine, School of Medicine, Medical College of Virginia, Richmond, Va.

cardia or by increased rate of velocity flow. Data obtained under basal conditions in five patients of 23 to 49 years of age with hookworm anemia illustrate the point in question (table 1). The subjects in table 1 were selected for study because of their ability to work as laborers without distress.

A review of the data in table 1 indicates that these individuals under resting conditions very likely did not have an increase in cardiac output, but were able to meet basal oxygen requirements by other mechanisms. The pulse rate averaged 70 per minute. The diastolic blood pressure was low, averaging 56 mm. The circulation time, sodium cyanide method, basilic vein–carotid sinus, averaged 19 seconds.

TABLE 1.—*Physiologic Data in Hookworm Anemia*

Age, Yrs.	Ht. Rate/ Min.	B.P. (mm. Hg)		Cir. Time (sec.)		Hgb. (Gm./ 100 cc.)	Venous Press. (mm. H_2O)
		Syst.	Diast.	A.C.*	C. Pul.†		
23	62	95	45	19	10	6.9	40
30	82	110	55	16	11	3.7	55
40	74	105	50	19	11	3.8	38
45	56	118	65	22	15	4.9	45
49	76	120	65	19	14	4.4	72

* Arm to carotid sinus circulation time, sodium cyanide method.

† Crude pulmonary circulation time.

If the volume of cardiac output per minute is determined by rate of cardiac filling and pulse rate, it is improbable that these patients had an increased cardiac output under resting conditions. However, when they were subjected to physical stress in the form of standardized exercise, the cardiac rate increased from 70 to 97 per minute. The diastolic pressure was unchanged, while the average systolic pressure increased from 110 mm. to 132 mm. Hg and the average circulation time decreased from 19 seconds to 11.8 seconds. Even though no cardiac output studies were done, we conclude that under basal conditions of rest no cardiac stress was caused by the anemia in these compensated individuals, but when they were subjected to physical stress, increased cardiac output operated jointly with other mechanisms to supply the increased demand for oxygen. The increased cardiac output results from an increased pulse rate, acceleration of cardiac filling, and increased stroke volume with no increase in peripheral resistance.

We suggest that tachycardia and increased velocity flow are not physiologically adapted to prolonged strain but rather are mechanisms to meet acute bodily stresses such as fever, exercise, hypermetabolism, and acute anemia.

A review of our accumulated clinical material impresses us with the significant difference in the state of the heart in the ambulatory, physically active, anemic patient, and the patient who is inactive and as a rule confined to bed with essentially the same degree of anemia. We have studied many ambulatory patients with severe anemia and gross cardiac enlargement who show rapid reduction in cardiac size following bed rest without significant change in the degree of anemia. We have not seen unequivocal myocardial hypertrophy, post mortem or by reliable clinical technics, in an anemic patient unless he had been physically active during most of the period of the anemic state, or unless some intrinsic cardiac disease or hypertension coexisted.

The most frequent symptom is dyspnea on effort. The vital capacity of the lungs is a simple, sensitive index of the pulmonary reserve available for augmented respiratory function. The greater the vital capacity, the greater the margin of reserve between comfortable and uncomfortable breathing when increased pulmonary function is necessitated by an augmented volume of pulmonary blood flow. We have found pulmonary ventilation consistently increased on exercise in anemic patients with hemoglobin of 7 Gm. per 100 cc. or less. This occurs in normal individuals, but the difference between the anemic and normal person is in the greater magnitude of increase in anemic individuals with an equivalent amount of work. This encroachment on respiratory reserve predisposes to dyspnea.

It is not surprising that a lowered vital lung capacity has been observed in many anemic subjects.[9, 10] With the passage of time in the completely acclimatized individual, ventilating capacity may be definitely increased beyond normal, approaching that of the athlete.[11]

Patients of this type are capable of much physical work even in a tropical climate in the presence of high degrees of anemia. To discuss the many biochemical and biophysical factors which operate in the dyspnea of the anemic patient is beyond the scope of this paper. A review of published data emphasizes the need for much additional work with special emphasis on the physiologic state of the adequately acclimatized anemic patient who, by virtue of the perfection of compensatory mechanism, can accomplish much physical work.

Individuals with parasitic and other chronic anemias may exhibit more intense pallor than the hemoglobin levels indicate. This is similar to the pallor of myxedema which is due not only to the changes in the quality of the skin but to a reduced peripheral circulation. Plethysmographic measurements of the extremities show diminished blood flow in the hands.[12, 13] Direct observations on the capillaries of the finger-nail fold in anemic patients show marked vasoconstriction[14]; the flow is slow. Our unpublished data are similar. The observations of Bradley and Bradley[15] indicate greatly diminished renal blood flow in chronic anemia consequent to localized vasoconstriction of the afferent arterioles supplying the nephron. The renal blood flow in anemia may be reduced to a third or a half; yet the amount of plasma presented for filtration per unit of time is almost normal because of the low hematocrit values. Nitrogen retention is consequently uncommon unless primary renal disease coexists; however, some impairment of tubular function is usual, probably as a result of anoxia.

These observations indicate that the state of the vascular bed is not constant but varies according to the need for oxygen in different areas of the body. The selective shunting of blood from areas of lesser physiologic importance to more vital ones is effective in maintaining physical fitness. Since there is normally abstraction of 90 per cent or more of the oxygen from the coronary blood during its passage through the myocardium, serious degrees of myocardial anoxia can be prevented in anemia only by great increases in the volume of coronary blood flow by the shunting of blood to this vital organ. That this does happen, there is little doubt, but direct observations on the volume of coronary blood flow in anemic patients both at rest and during stress of physical work are needed.

Numerous electrocardiographic studies in acute and chronic anemia indicate minor changes in approximately 20 per cent of the subjects. The changes are not specific for anemia and are usually minor in degree. Our observations and those of Hunter[16] reveal that in the few patients showing gross abnormalities, no improvement in the electrocardiogram occurred in spite of successful treatment of the anemia. A review of our cases of chronic parasitic anemia shows the interesting fact that of those patients with irreducible cardiac enlargement, 86 per cent showed electrocardiographic changes indicating left ventricular preponderance. This is not conclusive evidence of increase in muscle mass, but it is highly suggestive when correlated with irreducible enlargement.

The heart is the one organ which shows significant physical changes in chronic anemia. Bamberger[17] in 1857 concluded that cardiac enlargement was a frequent result of chronic anemia. Irvine[18] in 1877 and Barrs[19] in 1891 attributed the bruits in chlorotic anemia to cardiac dilatation. Gautier[20] in 1899 recorded his observations in 22 cases of chlorotic anemia and found cardiac enlargement by percussion in 20. Cabot and Richards[21] in 1919 observed cardiac hypertrophy in a patient dying of pernicious anemia in whom no other factor existed to account for the enlargement. In 1927, we studied a patient with hookworm anemia with hemoglobin of 2.9 Gm. per 100 cc. and a cardiothoracic ratio of 62 per cent. The heart size returned to a cardiothoracic ratio of 49 per cent when the hemoglobin increased to 14.6 Gm. per 100 cc. Ball[22] in 1931 was the first to report a case of severe anemia studied with the aid of a teleroentgenogram recording a reduction in heart size with the relief of anemia. Ellis and Faulkner[23] in 1939 studied 47 patients with varying types and degrees of anemia. Of the 38 cases studied by x-ray, 20 showed cardiac enlargement. Later observations in 26 of these patients showed decrease in heart size in 18, with im-

provement in the hemoglobin level. In 1937 one[11] of us reported the results of detailed studies on 18 cases of chronic parasitic anemia. It is significant to note that all of these patients were ambulatory and many were doing physical work. This study showed increased cardiac size in all these patients. The data indicated that the increase in heart size in a few patients was due to reversible dilatation; in others it was due to reducible dilatation and hypertrophy, and in a third group, to definite hypertrophy unassociated with reducible dilatation.

The potential ill effect of anemia on the diseased heart or on the heart laboring under the stress of hypertension, hyperthyroidism, valvular heart disease, pregnancy, arteriovenous fistula, or on the senile heart is a clinical problem of major importance. In many of these conditions high output failure is the rule. It is recognized that in these patients, relief of the failure is rarely satisfactorily accomplished until the condition responsible for the increased cardiac output is eliminated. The relief of anemia may be a deciding factor between recovery or intractable failure.

Many observers have reported the occurrence of angina of effort in patients with anemia.[16, 23-31] Complete relief of angina pectoris by appropriate treatment of the anemia has been observed. Such patients are admittedly rare and are invariably in the age group in which coronary arteriosclerosis is common. There have been several case reports of angina and anemia in which no evidence of coronary artery disease was found at postmortem examination. It is our conviction that in such patients the lumen of a small twig of a coronary artery was lessened by arteriosclerosis, which is difficult to demonstrate post mortem. As previously mentioned, the normally large utilization of arterial oxygen by the heart predisposes to ischemic muscle pain in the area supplied by an artery with a narrowed lumen and inelastic wall. The three patients reported by one of us in 1932 and four additional patients observed since then support our belief that angina of effort occurs in patients with anemia only when the coronary arteries are abnormal. Six of the seven patients were carefully followed. Four have died from coronary artery occlusion, one has had myocardial infarction, and one is of particular interest. This patient had pernicious anemia; he was temporarily symptom-free when the hemoglobin was 8 or more Gm., but for the past 14 months he has been unable to walk even slowly on a slight incline unless the hemoglobin is 15 or 16 Gm. per 100 cc.; this suggests progressing coronary artery disease. Our conclusion is that in the few patients who have the anginal syndrome associated with anemia and are rendered free of symptoms by relief of anemia, the complete diagnosis should be angina pectoris resulting from coronary insufficiency.

It is generally appreciated that a systolic murmur is frequently heard at the mitral area in anemic patients. Such murmurs occasionally are heard over the base of the heart at the aortic area, but more frequently over the second and third left intercostal areas. These murmurs are rarely accompanied by significant thrills, are best heard in the recumbent position, are increased in intensity by exercise or amyl nitrite inhalation, and are frequently associated with a snapping quality of the first cardiac sound quite suggestive of mitral stenosis. These elusive apical phenomena are found in their most significant form following the hemolytic crises of sickle cell anemia. Joint pains and fever frequently accompany the crises, resulting in a clinical syndrome quite similar to rheumatic fever and rheumatic heart disease. It is our impression that these signs are more closely related to the accelerated circulation and tachycardia than to the degree of anemia. The mitral signs are best heard when the bell of the stethoscope straddles the intercostal space and is lightly applied to the chest wall. As a rule the snapping quality of the first sound will disappear if the bell of the stethoscope is pressed firmly to the chest wall and against the lower margin of the rib rather than over the intercostal muscles; this is not observed in mitral stenosis.

Aortic diastolic murmurs accompanied by the peripheral phenomena of aortic regurgita-

tion are uncommon. Of the 34 anemic patients studied by Hunter,[16] only one had an early diastolic murmur. We have observed a diastolic aortic murmur with the vascular phenomena of aortic regurgitation only twice since our interest in the heart in anemia became intense about 1925. In both of these patients, the anemia was severe with hemoglobin values of 2.6 and 3.1 Gm. per 100 cc. In each case there was gross cardiac dilatation; the aortic phenomena disappeared with bed rest and reduction in cardiac size before there was significant change in the degree of anemia. The diastolic murmur and fever which frequently accompany severe anemia may suggest bacterial endocarditis or active rheumatic heart disease. Prompt change in the cardiac phenomena following bed rest and appropriate treatment of the anemia simplifies the differential diagnosis.

We agree with Hunter[16] that with the exception of aortic diastolic murmurs, there is no constant relationship between the degree of cardiac enlargement and systolic murmurs. It is our impression that the murmurs are more related to cardiac rate and velocity of blood flow than to either cardiac size or reduced oxygen carrying capacity of the blood.

In many anemic patients the physical signs and symptoms, including edema, strongly indicate heart failure of the congestive type. A detailed study of many such individuals has convinced us that congestive failure does not result from anemia in patients whose hearts are otherwise normal. If true congestive failure occurs with elevated venous pressure, hepatomegaly, orthopnea, and paroxysmal dyspnea, the coexistence of intrinsic cardiovascular disease is almost certain. The prognosis of congestive heart failure in the anemic patient is good, however, if the anemia can be successfully corrected.

Summary

The following brief summary seems justified from the large volume of accumulated data dealing with the reaction of the cardiovascular system in the anemic patient.

There are four mechanisms operating in the anemic patient which may increase the supply of oxygen to the tissues when the oxygen carrying capacity of the blood is reduced. Under conditions of rest, a rapid velocity flow and tachycardia with an increase in minute volume of cardiac output is the first response to anemia. As compensation develops, tachycardia and increased velocity flow are largely replaced by selective shunting of blood and the removal of an increasing percentage of oxygen in the tissue capillaries from each gram of circulating hemoglobin.

These later physiologic mechanisms are best illustrated by patients with chronic parasitic anemias. Under conditions of physical stress each of the four physiologic mechanisms contribute in meeting the demands for increased oxygen requirements. Compensation is, however, never perfect; the status of the patient is determined by the reduction in hemoglobin, the tissue oxygen requirements, the presence of physical changes in the cardiovascular and pulmonary systems, degree of oxygen abstraction from the blood, and the selective shunting of blood.

In relatively acute anemia, dyspnea readily occurs on physical exercise. Reduction in the ventilatory capacity of the lung occurring in some anemic patients results from an over-all reduction in physical fitness due to the anemic state rather than to physical changes in the lung. In well compensated, chronic anemia, the vital capacity of the lungs is frequently above normal and similar to that observed in athletes and completely acclimatized, high altitude inhabitants.

In the absence of cardiovascular disease or physical or metabolic factors requiring increased cardiac output, true congestive heart failure rarely results from the anemic state.

Effort angina is uncommon in anemic patients and when present is usually related to underlying coronary artery disease.

Cardiac hypertrophy under certain conditions results from prolonged anemia. Since cardiac hypertrophy is rightly placed in the category of organic heart disease, one is justified in classifying chronic anemia as one of the

etiologic factors in the production of heart disease.

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CLINICAL CONFERENCES

EDITOR: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

The Arterial Spider and Similar Lesions of the Skin and Mucous Membrane

By WILLIAM B. BEAN, M.D.

DR. BEAN: The topic for the conference today will be the arterial spider of the skin[1] and other lesions of skin and mucous membrane which sometimes cause confusion in the minds of physicians. As background for the discussion I will start with a short autobiographic note. This chronicle may help answer a question many students have asked me: "How did you get started in clinical research?" I do not recall having noticed or having had called to my attention the vascular spider of liver disease when I was an undergraduate student of medicine at the University of Virginia. When I was an intern on Dr. Longcope's service at the Johns Hopkins Hospital, both Dr. Longcope and Dr. Hamman commented casually upon the spider and remarked on its frequent association with chronic liver disease. Neither one was able to give me any references to medical writings on the subject, nor was their own information very extensive. When I went to the Thorndike Laboratory in Boston I again sought information on the significance of the spider and found that no one at that fountainhead of clinical research could give me any additional help. I inquired of Dr. George Minot, Dr. Soma Weiss, Dr. Chester Keefer, Dr. William Castle and many of their colleagues but was able to get no more information than in Baltimore. Following this, my migration westward began.

Arriving in Cincinnati, I found that the spider was well known. Dr. Blankenhorn was able to add a certain amount of information, but I am especially grateful to him for giving me access to a great many patients for what observations I chose to make.

Before this phase of the story goes too far I would like to have Dr. Mitchell tell us about a girl from the Pediatric Service.

DR. RICHARD C. MITCHELL: H. R., a 12 year old white girl, was admitted to the Pediatric Service on Jan. 29, 1953 with the diagnosis of recurrent hepatitis. She had a history of repeated episodes of jaundice over the past two years. She had been in good health until two years ago when she developed diarrhea, vomiting, and a slight fever. Four days after the onset of the illness her family noticed that she was becoming jaundiced. Her urine was a dark amber color, and her stools were clay-colored. She was kept in bed and given a high carbohydrate diet for three weeks. At the end of this time her jaundice had faded and she was allowed full activity. No inoculations had been given and no other skin punctures done prior to the onset of the illness. Approximately 12 other people in the same community had a similar illness at the same time. Since the first episode two years ago she has had four or five similar attacks. The most recent began during the latter part of December and continued through the time of her admission to this hospital. Normal activity has continued between the attacks. Her appetite has decreased somewhat. Her health, in general, has been excellent between the episodes of jaundice. She has not yet reached the menarche.

Physical examination upon admission to the hospital revealed a 12 year old girl with 2 plus icterus of skin and sclera. Arterial spiders were noted on both hands and on the right anterior thigh. There was no palmar erythema. The liver and spleen were both palpable 4 cm. below the costal margins. They were not tender and revealed no irregularities. The breast development and pubic hair were average for her age. Axillary hair was absent.

From the Departments of Internal Medicine, Pediatrics, Dermatology and Obstetrics, College of Medicine, State University of Iowa, Iowa City, Iowa.

Her course in the hospital has been uneventful. She has been afebrile. Her jaundice has remained unchanged. Her stools have continued to have a clay-like appearance and the urine a dark, amber color. Her appetite has been good and her general demeanor excellent. Many additional spiders have appeared on the anterior chest, neck and face.

Laboratory examinations at the time of her admission were as follows: The urine was dark amber in color, negative for blood, albumin and sugar; microscopic examination showed bile stained crystals, and urobilinogen was 4 plus. Blood studies showed 9.5 Gm. hemoglobin, 3.5 million red blood cells, and 3,150 white blood cells. The total protein was 9.3 Gm. per 100 cc.: fibrinogen was 0.7 Gm., albumin, 1.7 Gm., and globulin, 6.9 Gm. The van den Berg test gave 16.3 mg. per 100 cc., direct, and 27.5 mg. per 100 cc., indirect. The cephalin flocculation test showed 4 plus in 24 hours and 4 plus in 48 hours. The thymol turbidity test was 15.1 units. Total cholesterol was 98 mg. per 100 cc., cholesterol esters 27 (27 per cent).

DR. BEAN: To those of you in the front rows the lesions appear as red spots. Pulsation is felt easily in the larger spiders and may be seen when a glass slide compresses the surface. The spider on the thigh is much lower on the body than is usual; and when they are found below the level of the navel there are many others in the blush area of face, neck and upper chest. The standard texts on pediatrics and monographs on liver disease in children have echoed with stubborn persistence the error that children with chronic liver disease do not get spiders. This is utterly wrong.

To get back to the story, in Cincinnati Dr. Donald Foster, Dr. Morton Hamburger and I undertook a very extensive study of the natural history of the vascular spider. We collected a great many cases, made numerous observations on the size, location, distribution and type of lesion in chronic liver disease and accumulated a very formidable body of material. What began as an interesting hobby became a fascinating theme for speculation and thought. We had many discussions. Since my interest in spiders was well known it was not surprising that several members of the intern and resident staff whose wives were pregnant came to me in a state of great concern when their wives developed spiders during pregnancy. Their only thought was that these might be some ominous indication of liver disease or perhaps even the dreaded acute yellow atrophy occasionally observed during pregnancy. Since I knew nothing of the significance of such vascular changes in the skin I advised a course of optimistic waiting. All the pregnancies turned out well. Since the children born were completely normal it dawned on us that the acquired arterial spider might occur as an apparently banal and insignificant complication of normal pregnancy as well as a stigma of chronic parenchymal disease of the liver.

In addition to the characteristic vascular spiders a number of other lesions such as the telangiectatic mat, paper money skin, changes in the vascular structure of the nose, palmar and occasionally plantar erythema were all noted. Many observations and studies failed to reveal any clinical or laboratory test which had any regular correlation with the emergence of vascular spiders. Their curious association with pregnancy became a mild obsession in my speculations. The one common denominator which was fairly well established between normal pregnancy and the state prevailing in chronic parenchymal disease of the liver was an increased urinary excretion and presumably an increased blood level of estrogens. By analogy it was not very difficult to suppose that potent steroid hormones might have an effect on blood vessels in the human skin as well as their classic and much studied effect upon the spiral arterioles of the endometrium and myometrium. This analogy was given some support by the physical structure of the spider which turned out to be a curious admixture of arterial and vein-like components. On the basis of these speculations powerful estrogens were given to several patients with cirrhosis who had recovered clinical well-being but still had residual liver damage. Some developed new spiders and palmar erythema. At this stage of the work I began to do systematic reading on the subject. There was a very considerable body of literature tucked in out-of-the-way places and to my surprise I found that many of the observations I had made were already recorded in medical writing in one place o-

another. It is fortunate when clinical observation is allowed to run the early stages of its natural course uninfluenced by previous views and experience as recorded in medical writings. One thus has freedom from the bias of others although he must deal critically with his own bias. Among the things I found was a description by Erasmus Wilson, one of the first English specialists in dermatology. He described the vascular spider in an elegant, brief note which had remained buried for about 70 years. This note is short enough to read here in full. I call your attention to the fact that the man was a publican, that is a bartender, rather than a Republican which I cannot define.

"A publican, aged 30 years, had for some time yielded to the temptation of his calling, and had thereby injured his health, when he was suddenly attacked with epistaxis and to the epistaxis succeeded copious bleeding from the gums. After some time, and subsequently there appeared on the face, the neck, the hands, and the arms, an eruption of red papulae with a diffuse areola. On presenting himself for consultation there were six of these papular spots on the face, chiefly on one cheek, two on the neck and three or four on the hands and forearms. It was evident, on careful examination, they were angiomata; the central prominence was vascular, and around this was a plexus of venules spreading out to the breadth of a quarter or half an inch. In one or two of the spots the central prominence was absent and a plexus alone existed, resulting from angiectasia, or multiplication and hypertrophy of the venous capillaries of the skin. The case is very rare, a sudden eruption of angiomata, and its association with hemorrhage from the mucous membrane of the nose and mouth is very instructive. We are unaware of the conditions of the economy which may tend to the sudden hypertrophy of blood vessels, but we can easily understand how such an occurrence, taking place upon the mucous membrane, might lead to serious hemorrhage; and there is no reason to suppose that the cause of the epistaxis in the instance before us, and the bleeding of the gums may not have been a sudden hypertrophy of blood vessels such as we have just described as appearing on the skin. And it appears to us that as a result, to the well-known hemorrhagic diathesis as a cause of hemorrhage there must also be added a sudden hypertrophy of blood-vessels and rupture of their coat as exemplified in the case before us."

A great deal had been added to the knowledge of vascular spiders by French observers Hanot and Gilbert, Steinmann, Emile-Wile and more recently in this country by Patek and his co-workers, Williams and Snell, Walsh and Becker and many others.*

Jonathan Hutchinson, whose masterful observations on syphilis are remembered in the name Hutchinson's teeth, has a little note in his Archives of Surgery, that magnificent repository for rare and unusual dermatologic lesions, about the occurrence of spiders as blemishes. He believed that they affected women primarily although he suggested that perhaps vanity was the reason why he saw more women than men with such lesions. In any event he established clearly the fact that they might occur in perfectly normal people and this point must be emphasized since arterial spiders are of clinical significance only when new ones appear, old ones enlarge or when they are numerous. Many people we consider perfectly normal have one or a few vascular spiders, frequently on the face near the eyes. Some notice them occasionally coming and going on the lower arms and back of the hands. Corbett, in a very brief note, referred to them in normal pregnancy as early as 1914 although this information and the additional occasional notices of them in pregnancy were never transferred by the specialists in dermatology to those in obstetrics. There is no mention of them until quite recently in American textbooks on obstetrics.

I confess to being the inadvertent source of an error which prevailed widely in the 1940's, a supposed connection of the arterial spider with deficiency diseases. During the spring and summer of 1940, 1941, and 1942 I had the opportunity of working in the nutrition clinic at Birmingham. There I devised the first record form for keeping observations on all the numerous patients with deficiency diseases. Because of my interest in spiders and palmar erythema I included in the chart for recording physical signs a place for observation on such lesions and I made systematic notes on about 700 patients with reference to arterial spiders and palmar erythema. My thought at the time was that this might be a relatively normal

* The references cited are included in the three papers referred to in the references.

population as far as liver disease was concerned. I found a great many subjects who had one or a few spiders but except for those who were pregnant or the few who had liver disease they never occurred in any considerable number. Furthermore they varied, coming and going erratically without any relationship to the nutritional state of the patient or the specific dietary and vitamin therapy. Visitors to the nutrition clinic, of whom there were many, used the record sheet as a model and, apparently supposing that whatever was found in the record of physical examination in a nutrition clinic must have some bearing on nutrition, the assumption was made that arterial spiders and palmar erythema had some definite although not fully understood connection with deficiency disease. I was astounded to find numerous subsequent reports attaching a nutritional significance to spiders. This persists to some degree although I have tried to correct this error.

As for palmar erythema,[2] it too has a remarkable history. The first clear description was given by Chambers in 1899 in a brief note in the Lancet in which he described such a red color of the palm as commonplace among white inhabitants of the Gold Coast. It later was described completely independently by Lane as a familial or hereditary stigma of no significance to the patients concerned. Classic observations connecting palmar erythema and arterial spiders were made by Walsh and Becker whose paper gives the first illuminating study of a connection of these two lesions and their rather common occurrence in pregnant women. Apparently palmar erythema was recorded in pregnant women the first time by Forman in 1934. In this connection I should like to mention the fact that, in our original observations of patients with spiders, in several of my notes there are detailed descriptions of the anomalous color of the hands, its strange pattern, the increased warmth of the erythematous area and its association with spiders in chronic parenchymal disease of the liver. This observation must have been made almost mechanically since I thought nothing of it until reading the paper by Walsh and Becker at which time I went back to the records and found that I had been looking at the same sort of thing for four years without seeing it. Description of liver palms or palmar erythema in chronic liver disease appeared nearly simultaneously in 1942 and 1943 in papers written by Ratnoff and Patek, Perera and myself.

There are two distinct varieties of palmar erythema. The first is simply an exaggeration of the ordinary speckled mottling of the palm and is diffuse without regular regional accentuation. In the more common type of "liver palms" the area of most intense redness is the hypothenar eminence and the next most common is the central aspect of the thenar eminence. In the region where the fingers join the hand there are apt to be islands or spots of erythema not directly under the palmar calluses but between them. The next most common area of redness is the palmar surface of the fingertips, and when the condition is extreme the process extends around on the back of the fingers in a horseshoe-like arrangement at the base of the nails. There may be a considerable variation in intensity of the red color from time to time. Characteristically it is bright red, but there may be some irregularity and at times there are cyanotic spots. Ordinarily there is a sharp line of demarkation between the red and the uninvolved skin. Minor variations in palmar redness are frequent. The correlation between severe chronic liver disease and palmar erythema is not as close as between severe liver disease and arterial spiders. If one analyzes the records from a large series, those with liver disease who have spiders are about twice as apt to have palmar erythema as those who do not. Contrariwise, those who have palmar erythema are about twice as apt to have spiders as those who do not. Obviously either may occur without the other, but their frequent association makes it seem likely that they are produced by the same general force. The distribution of the palmar and sometimes the plantar redness suggests that perpetual dilatation of glomus bodies may be responsible for the striking and fairly consistent pattern. These points remain to be established by further studies.

At this stage all my observations on spiders

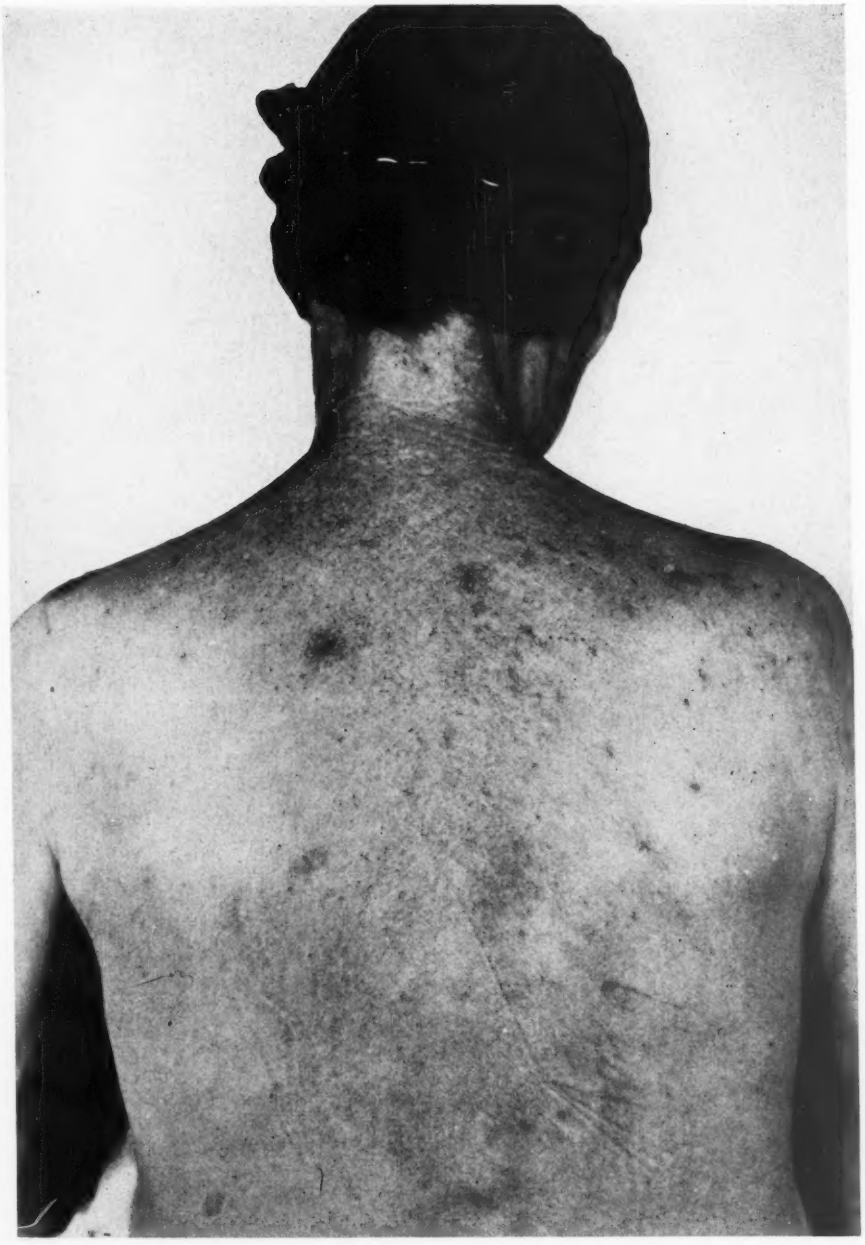

FIG. 1. Arterial spiders and paper money skin.

ame to a halt when I joined the Army and egan working on tanks, adaptive physiologic rocesses in soldiers and many kinds of environment—fascinating topics which were well away from clinical medicine. The time in the Army did, however, give an unexcelled op-

FIG. 2. Arterial spiders and pigment marks.

portunity for reflection and speculation, so that all the observations on several hundred patients and normal people were gathered together. Cullings from an extensive review of medical writings from approximately the hundred year period from 1845 to 1945 were

added. Furthermore I had the opportunity to write and rewrite a monograph on what was now for me a favorite topic, though one so far off the beaten path that I thought it too would be entombed with other observations on the arterial spider.[1] I had, however, the fabulous luck of having it published at the end of World War II when, as you all know, hepatitis rather than influenza had proved to be the major epidemic of concern during the war. Liver disease and spiders were not only a timely topic but one of intrinsic importance. Having indulged a most esoteric and seemingly not useful or practical field for a medical hobby, I hit the jack-pot.

FIG. 3. Scale outline of actual arterial spiders.

The arterial spider, as the name suggests, is characterized by a body and legs (figs. 1 and 2). It has a surrounding erythema. The body or central point may be small or so large as to attract immediate notice. There is usually a relationship between the size of the body and the size of the whole lesion (fig. 3). There is a tendency for the body of the larger ones to become elevated, rarely as much as 0.5 cm. above the adjacent skin surface. Such lesions may be seen to pulsate. Palpable pulsation is found uniformly and may be demonstrated readily by applying a glass slide to the lesion and adjusting the pressure. Branching legs or radicles radiate from the central hub, spread out just under the plane of the skin and parallel to it. They may be clearly defined and relatively large or may be very numerous and hard to distinguish. Indeed some lesions present nothing more than a diffuse erythema. The vessels branch and become smaller fading out at the periphery. An area of erythema surrounds the central punctum and usually encompasses the visible radicles. The whole lesion may be roughly circular although the star and cog-shaped lesions are common. The color of the spider is characteristic of the abundant arterial blood. It is bright, fiery red. The temperature of the spider may be as much as 3 C. higher than the uninvolved adjacent skin. Blood flows centrifugally from the body in all directions towards the periphery. This may be demonstrated when the spider is blanched by pressure with a pencil point or the finger and then suddenly released. Filling is from the center outward. Pulsations can be demonstrated most easily when spiders occur over bony structure such as the forehead, sternum or clavicle. The arrangement of collecting veins is that usual in the skin. In histologic preparations there are no venae comites. Spiders are rare in the scalp, rare in the axilla and other hairy regions although they may occur in the beard or on a hairy chest. Spiders have a very curious distribution with remarkable *concentration around the face, the neck, upper portion of the chest* and a diminishing concentration over the shoulders, the lower chest, upper and lower arms and dorsum of the hand (fig. 4). They are rare on the palms though they do occur. In spite of the girl we just saw they are notably rare in the body below the level of the diaphragm. I have never seen spiders below the diaphragm when they were not more numerous and larger in the upper portion of the body. That they occur in the lower extremities at all suggests that the factors governing their distribution are relative and not absolute.

A STUDENT: Why are spiders so rare in the lower parts of the body?

DR. BEAN: I do not know. My speculation is that a humoral force and susceptible vascular structures are necessary. Since spiders are rare where the vasomotor gradient in the skin indicates a high degree of vasoconstriction, a humoral agent might not have time enough to produce its effect. Why don't you make that

a project to work on? We know very little of the exact pattern of distribution of many skin lesions, and even less about their cause.

Associated skin changes include paper money skin in which a number of readily seen small vessels are scattered in random fashion comparable to the silk threads in American paper money. The frequent occurrence of palmar erythema in people with many vascular spiders suggests that the forces which give rise to the one give rise to the other, although there is by no means an exact correlation and one kind of lesion may occur without the other. Shock-producing hemorrhage causes the lesions

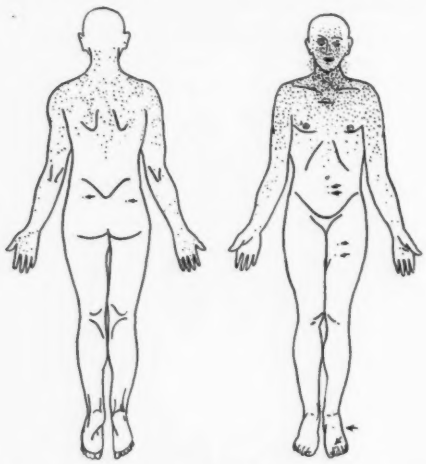

FIG. 4. Distribution of spiders in hepatic disease: A composite of 793 individual lesions from 41 patients.

to fade, and they may be seen first only after transfusion has restored blood to normal.

A STUDENT: Do such lesions occur anywhere besides in the skin?

DR. BEAN: Similar vascular abnormalities occur in the mucous membranes of the nose, the mouth, the pharynx, the hard and soft palate and probably along the mucosal lining of the alimentary canal. They may occur throughout the interior of the body but this point cannot be established since their post-mortem fading prevents conclusive evidence being brought to bear on this point. Spiders disappear frequently and fade invariably after death.

A PHYSICIAN: Do they occur in families?

DR. BEAN: Family history for spiders may be positive, particularly if one can examine members of several generations. Most people are poor observers and do not know that other members of the family have them. Spiders vary in number and size in relationship with the clinical course of cirrhosis. As the disease improves they may fade or disappear and their fading suggests that clinical improvement is in the offing. They tend to occur in outbursts or increase in size at a time when liver failure is increasing. In pregnancy they tend to appear

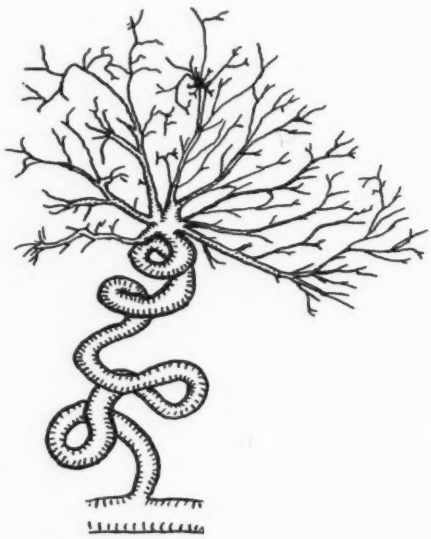

FIG. 5. Schematic diagram of arterial spider.

between the second and fifth months.[3] They increase in size and number throughout gestation, disappearing just before delivery or during the puerperium. Large ones may persist.

A STUDENT: What pressure exists in the spider?

DR. BEAN: Pressure within the arterial spider is somewhere between 60 and 100 mm. Hg as measured directly by applying a capsule to the lesion and connecting it with a mercury manometer.

QUESTION: What is the histopathology of the spider?

DR. BEAN: Histologically there are two kinds of spiders. One apparently is simply an over-

grown end-artery in the skin. The other is a thickened, coiled artery in the subcutis much larger than those generally found in this region (fig. 5). In the walls are aggregations of glomus cells, the pericyte of Zimmermann, ancestor of ordinary vascular smooth muscle cells. They are irregularly disposed along the vessel wall and may occur in beads or bands. At the punctum there is an abrupt thinning of the wall which breaks up into numerous vessels which are vein-like, having very thin walls but, nonetheless, carrying arterial blood peripherally out to the capillaries and the venous collecting system. Thus the arterial spider is an overgrown end-artery usually containing many glomus cells in the walls of its major central artery and paradoxically it breaks up into many vessels which while carrying arterial blood have the structure of veins.

Venous Star

A Student: Are there other lesions in the skin which may be confused with the spider?

Dr. Bean: A lesion which only occasionally gives rise to confusion with the arterial spider is the venous star[4] which is found in association with persistent elevations in venous pressure. At times they have a very close resemblance to arterial spiders. The stars usually overlie and are tributary to a vein of large size. Blood flows from the periphery of the star centrally and thence into the collecting vein; the direction of flow is the exact opposite of that in the arterial spider. The pattern, shape and size are much more variable than in the arterial spider. Although the color frequently is blue, in some instances it is bright red and in such circumstances the lesion may have a close resemblance to the spider. Most characteristically these lesions are seen to develop where new collateral veins are enlarging after obstruction of the superior vena cava. At first one may notice only a blue discoloration of the skin, but after a few days or weeks the characteristic star form appears with an irregular central spot, either blue or red, not much elevated above the skin. They may be 2 or 3 inches in diameter. Skin temperature is not higher than over adjacent skin. They are obliterated with pressure. They fill by reflux from their underlying vein. Thus filling is centrifugal, the same as in the spider, but the blood flow is reflux and reversed from the usual direction. Although stars commonly occur along the lower borders of the ribs, they do not follow the anatomic insertions of the diaphragm nor the juncture of the abdominal and costal wall. They are common on the dorsum of the feet, around the ankle and the lower legs both front and back, and above the knee on the medial aspect of the thigh. Smaller ones are apt to appear on the back just at the junction of the neck and thorax and over or just above the region of the sacrum, particularly in women. They are common only after adolescence, but

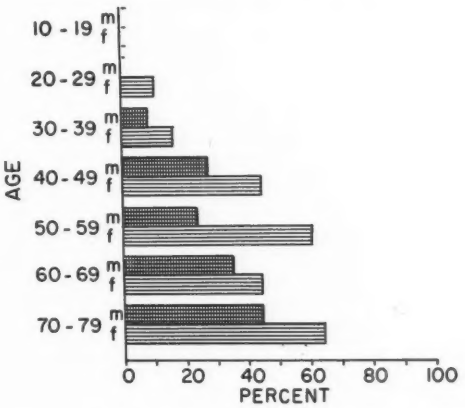

Fig. 6. Incidence of venous stars by sex and decade.

they may occur in children, particularly where some lesion produces an extensive collateral venous circulation (fig. 6). They are more common in women than men. I have seen stars develop over a period of 10 days and seen them disappear over a period of one to two months. Histologically they are dilated veins.

Osler's Disease

Dr. Bean: Another lesion which we have considered in some detail in a recent clinical-pathological conference is the telangiectasis of Osler's disease or hereditary hemorrhagic telangiectasia.[5] Ordinarily this lesion in the skin is punctiform, usually flat but sometimes a little elevated. It has very sharp margins which separate it from the adjacent uninvolved

skin. Occasionally a single vessel is connected with the punctum. Sometimes there are several which gives it a close superficial resemblance to the arterial spider. Pulsation is usually harder to demonstrate than in the arterial spider. Solid cyanotic looking nodular forms exist. The mucous surfaces of the body may have a much thicker concentration of lesions than does the skin. They may exist in any part of the skin although they occur in the upper portions of the body more often than over the legs or feet. Mucosal telangiectases may be seen in Kiesselbach's area in the nasal septum, at the tip and dorsum of the tongue, palate, pharynx and esophagus. Hemorrhages from the stomach, bowel, lung, brain, bladder, kidney and liver attest their universal range. They are very frequent on the palmar surface of the hands and fingers, common in the nail beds, the lips, and the ears (figs. 7 and 8). A history of bleeding in the family is invariable and the trait is inherited as a dominant characteristic. It is not sex-linked. Hemorrhage from these lesions, part of the Latin title, occurs with varying frequency and intensity. In mild instances of the disease bleeding is relatively infrequent and not very troublesome. In others continual bleeding is an ominous problem and never-ending hazard. The age at which bleeding begins varies. Nose bleeds in childhood, a period free from hemorrhage, or the reappearance of frequent hemorrhages at puberty or in the third decade when the telangiectases begin to become numerous should cause strong suspicion of the underlying disease. The pathologic alteration in Osler's disease is a thinning out of the wall of the vessel, the loss of muscle and elastic tissue with a bulging and ballooning of the wall, and the development of tortuous coiled masses of tiny aneurysmal vessels including capillaries and small veins and arteries. Skin temperature over the lesion is not higher than over adjacent skin. Pulsation is rarely felt but occasionally can be demonstrated vividly, particularly when capillary pulsation exists. The existence

FIG. 7. Skin lesions in Osler's Disease: The palm and fingers.

and growth of pulmonary arteriovenous aneurysms has thrown a new light on the dynamic state of this vascular anarchy.

Cherry Angioma

A Student: Are any other skin lesions mistaken for spiders?

Dr. Bean: Yes. The lesion called cherry angioma, or ruby spot, sometimes known as capillary angioma, senile angioma and in English medical writings referred to as De-Morgan's spot has been confused with the spider at times. Since such lesions appear at early age and are relatively frequent after adolescence, it is best to drop the name "senile angioma" and call them by some purely descriptive name such as "cherry angioma" or "ruby spot." No one has demonstrated a familial tendency, but this point is hardly pertinent since they are found almost universally in elderly people and are quite common in early ages. The incidence rises sharply in the 30's so that approximately three-fourths of the persons observed after the age of 30 have such lesions. Thereafter they increase in frequency and in the 60's and 70's they are found almost universally.

Spontaneous hemorrhage has not been observed although occasionally injury to the angioma gives rise to very modest bleeding. The size and shape vary, but the characteristic lesion is small and flat during its early life, later increasing in size, becoming elevated with a dome or even a mushroom-like overhang. Rarely, they become so large that they are attached by a pedicle. In persons with the characteristic large lesion, small ones may be found, and, using magnification of 20 times, many lesions which escape inspection by the naked eye are brought into view. Such magnification reveals that the angioma is composed of numerous dilated loops which appear as quite separate vascular channels at the margin and are somewhat jumbled together in the center. Pressure on the individual lesion induces only mild and very slow blanching with some deformity, and the color returns slowly as the vessels fill and the natural shape is resumed. No pulsation is seen. An anemic halo of pallid skin surrounds many cherry angiomas and sets off their color in striking fashion. The color of the lesion is a bright cherry or ruby red, different from the fiery red erythema of the arterial spider. In the presence of cyanosis, angiomas over the upper part of the body may be a deep blue color. In the very old people

Fig. 8. Skin lesions in Osler's Disease. The nails and fingers.

with old lesions there is some atrophy and fading or the color tends to be tinged with a brownish element. The size varies from lesions visible only with magnification to rare instances where the lesion is more than 1 cm. in diameter and attached to the skin by a pedicle. The skin temperature is slightly but probably not significantly lower than that of the adjacent skin.

Distribution of cherry angiomas in patients between the ages of 50 and 80 are demonstrated in figure 9 which should be compared with figure 3 of the distribution of arterial spiders. There are the following differences in distribution: The cherry angioma is much rarer on the face and neck and there are proportionately more on the back. They are quite common on the abdomen, relatively common on the lower part of the body. They are not as common on the upper and lower extremities as they are on the trunk. Rarely they occur in hairy portions of the body and a few have been observed in the scalp. The number of individual lesions vary from zero to as many as 300 I counted in one patient. Usually there are somewhere between 10 and 50 in older subjects. The changing incidence with aging is seen in figure 10. No connection with any particular underlying disease has been noted in a series of observations of approximately 1000 patients seen in the office and on the medical wards during the past 18 months.

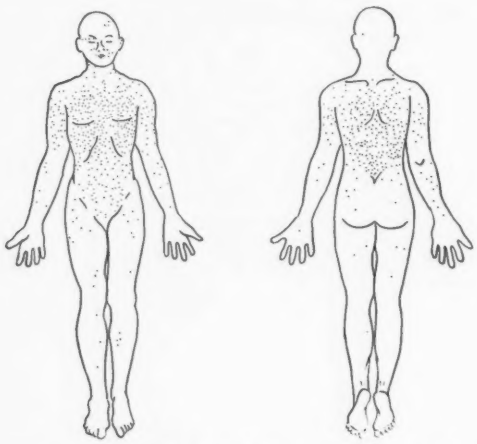

FIG. 9. Distribution of cherry angioma in adults aged 50 to 80. Compare with figure 4.

DR. CHARLES MAY: Have arterial spiders been observed in persons getting large doses of estrogens?

DR. BEAN: Where patients are treated for menopausal symptoms and where large doses of estrogens are given for carcinoma of the prostate, the development of many new spiders has not been observed. This may be because they are not looked for. Or they may not occur. I have hunted for them in a few cases and not found them, but a systematic study is needed to settle this very searching question.

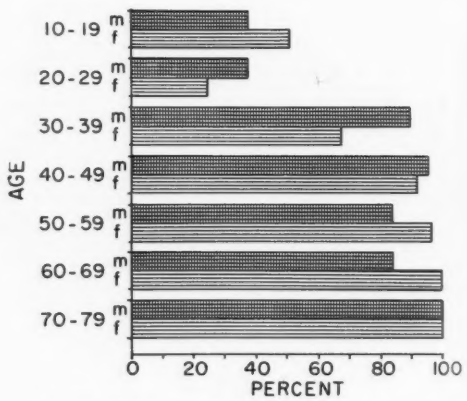

FIG. 10. Incidence of cherry angioma by sex and decade.

DR. RUBIN NOMLAND (Professor of Dermatology): Before Dr. Bean made his series of classic observations, spider nevi belonged to the dermatologist. We are often consulted about them, and of course can remove them with the electric needle. They may recur if not completely obliterated. A good many fall into the class of ordinary birthmarks and they are fairly common, especially in children and young adults.

DR. ROBERT DUFF: What is known about the nerve supply of the spider? Do they have sympathetic fibers?

DR. BEAN: I know nothing. My collection of many serial sections from about 25 spiders was lost during World War II and I have not studied the nerves.

Are there any more questions? If not, we may summarize briefly: the eruption of new spiders, or enlargement of old ones marks the advent or worsening of chronic parenchymal disease of the liver. Spiders are uncommon in obstructive jaundice but may appear late in the disease. In pregnancy they tend to appear from the second to the fifth month, sometimes fading out several days before delivery, usually fading at the time of delivery and during the early postnatal period. I have suggested that steroid hormones, especially estrogenic ones lead to this overgrowth of vessels in the skin. Their structure, distribution, histology and physiologic features have been indicated briefly.

Characteristics whereby they are differentiated from venous stars, Osler's hereditary hemorrhagic telangiectasia and the cherry angioma have been outlined. This being the first time in five years of these conferences that I have dared speak about spiders, I hope I will be pardoned for an intensely personal point of view. It may give a clue to one approach to clinical research which should stimulate and perhaps comfort those whose picture of clinical science has held only bubbling retorts, Geiger counters and ultracentrifuges.

Finally, in accordance with our custom of ending these conferences with a light note, I will bring you up to date on the latest variant on Mother Goose:

An older Miss Muffet
Decided to rough it
And lived upon whiskey and gin.
Red hands and a spider
Developed outside her—
Such are the wages of sin.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Zendel, J. F., and Lubart, A.: Diphtheroid Subacute Bacterial Endocarditis Successfully Treated with Bacitracin. Arch. Int. Med. **90:** 562 (Oct.), 1952.

In a case of subacute bacterial endocarditis due to a diphtheroid bacillus, treatment with bacitracin alone was successful after previous therapy with large amounts of other antibiotics singly and in combination had failed. Bacteriologic investigations were carried out to establish the causative organism as a true diphtheroid. A total dose of 1,860,000 units of bacitracin was given parenterally over a 31-day period without evidence of any serious or permanent toxic effects. A review of the literature has not disclosed another case of cure of subacute bacterial endocarditis with use of bacitracin alone. Elevation of temperature was noted during the first week of bacitracin therapy; this may have been a side-effect of its parenteral administration.

BERNSTEIN

Lepeschkin, E.: On the Relation between the Site of Valvular Involvement in Endocarditis and the Blood Pressure Resting on the Valve. Am. J. M. Sc. **224:** 318 (Sept.), 1952.

The incidence of endocarditis involving each valve in 1024 published autopsied cases was determined from the literature. The mitral valves were involved in 86 per cent, the aortic valves in 55 per cent, the tricuspid valves in 19.6 per cent and the pulmonary valves in 1.1 per cent of the cases reported. The average blood pressure exerted upon the mitral valve was calculated to average 116 mm. Hg, being the left ventricular systolic pressure. The pressure exerted upon the aortic valve is equivalent to the diastolic pressure, averaging 72 mm. Hg. The pressures resting upon tricuspid and pulmonary valves were calculated to be 24 mm. Hg and 5 mg. Hg respectively. It was concluded that the pressure acting upon the valve is the chief factor in determining the involvement of the valve in endocarditis. Several factors may operate in producing this relationship: (1) the mechanical force exerted upon blood-borne bacteria forcing them into the endothelial lining of the valve, or (2) the effect of mechanical stress upon the connective tissue elements of the valve altering the reaction to allergic and inflammatory processes.

SHUMAN

BLOOD COAGULATION

Friedman, I. A., Schwartz, S. T., and Vincenti, M.: Survey of Clotting Tests for Coagulation Profile in Normal and Diseased Persons. J.A.M.A. **150:** 83 (Sept.), 1952.

By means of a battery of tests including the Lee-White heparin retardation, and protamine heparin titration clotting times, the prothrombin determination, and platelet counts, a survey was made of clotting tests. This was done to obtain the coagulation profiles of normal persons as well as of patients with carcinoma, tuberculosis, leukemia, lymphoma, thrombocytopenia, polycythemia, and aplastic anemia. There was extreme variation in the range of values observed in all groups. In view of this wide variation, the authors believe that the Lee-White heparin retardation, and protamine heparin titration clotting times serve little if any useful function in evaluating bleeding and clotting tendencies. The relationship of the platelet count and the bleeding and clotting mechanism awaits further elucidation.

KITCHELL

Vander Veer, J. B., Parker, A. P., and Boyer, F. R: Emergency Appendectomy in a Patient Receiving Anticoagulants for Myocardial Infarction. J.A.M.A. **149:** 1307 (Aug. 2), 1952.

The present widespread use of anticoagulant drugs for treatment and prophylaxis makes it probable that an occasional patient's treatment will be complicated by the necessity for emergency operation. The authors report a case of acute appendicitis in a patient receiving anticoagulants for acute myocardial infarction. They discuss management and rapid preparation of the patient with vitamin K_1 oxide and citrated whole blood. Recovery was relatively uneventful and on the third day postoperatively the dosage of anticoagulant was resumed.

KITCHELL

Stragnell, R.: Intravenous Emulsified Vitamin K_1 in the Treatment of Coumarin-Induced Hypoprothrombinemia. Am. Heart J. **44:** 124 (July), 1952.

The author reports the reversal of coumarin-induced hypoprothrombinemia in seven patients by the intravenous administration of a stable nontoxic emulsified vitamin K_1 preparation. Bleeding ceased within three to four hours of the administration of the drug, and prothrombin level rose significantly from values of less than 10 per cent to 35 to 110 per cent within 11 to 19 hours. Dosage varied from 75 to 300 mg. In three patients when coumarin therapy was reinstituted, following the administration of vitamin K_1, resistance to the reinduction of hypoprothrombinemia was observed. This presents a serious problem where continued anticoagulant therapy is desired. This can be controlled by the administration of heparin with the coumarin drugs to safeguard the patient in whom the continuation of anticoagulant therapy is desired. In two instances death occurred after reversal of the hypoprothrombinemia. In one, extension of a coronary occlusion and myocardial infarct was demonstrated.

HELLERSTEIN

CONGENITAL ANOMALIES

Bing, R. J., Lombardo, T. Y., Bargeron, L. M., Taeschler, M., and Tuluy, S.: Congenital Heart Disease: A Clinical and Physiologic Correlation. Ann. Int. Med. **37:** 664 (Oct.), 1952.

Three examples illustrate the advantage of a stepwise, selective differential diagnosis of congenital cardiac anomalies based on physiologic, radiologic and clinical considerations. Although physiologic studies are not always essential for the diagnosis, such studies, by providing information relating to the hemodynamics of congenital heart disease, offer a rational diagnostic approach. In the first case catheterization demonstrated a gradient in oxygen content between blood from the superior vena cava and the right auricle, indicating the presence of an auricular defect. The aorta was intubated from the right ventricle, indicating a dextro position of the aorta. The pressure in the right ventricle was 118/10 and that in the pulmonary artery 16/11, demonstrating pulmonic stenosis. The arterial oxygen saturation was 72.5 per cent. The over-all intracardiac shunt was calculated to be 2600 cc., directed from right to left. On the basis of these findings, a diagnosis of tetralogy of Fallot with interauricular septal defect was made. In the second case there was a gradient in oxygen content from right auricular to right ventricular blood, suggesting the presence of a ventricular septal defect. The systolic pressures in the right ventricle and the pulmonary artery were approximately equal and markedly elevated. The intracardiac over-all shunt was calculated to be 300 cc., directed from right to left. The total right-to-left shunt was 880 cc. and the total left-to-right shunt 580 cc. The peripheral arterial oxygen saturation was 88 per cent. These findings confirmed the clinical impression of Eisenmenger's disease. In the third case the oxygen contents of blood withdrawn from the superior vena cava, the right auricle, the right ventricle and the pulmonary artery were equal, demonstrating the absence of a left-to-right shunt. A right-to-left shunt was also absent, since the arterial blood was fully saturated. There was a large gradient between the right ventricular and pulmonary artery pressure. These findings confirmed the clinical impression of isolated pulmonary stenosis.

WENDKOS

Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: Further Studies on the Treatment of Congenital Adrenal Hyperplasia with Cortisone. III. The Control of Hypertension with Cortisone with a Discussion of Variations in the Type of Congenital Adrenal Hyperplasia and Report of a Case with Probable Defect of Carbohydrate-Regulating Hormones. J. Clin. Endocrinol. & Metab. **12:** 1015, 1952.

Although hypertension is frequent in Cushing's syndrome, it is uncommon in the adrenogenital syndrome. The authors report on three cases of the latter syndrome with hypertension who were treated with cortisone. The first patient was an 18½ year old pseudohermaphrodite with persistent hypertension, which did not respond to salt restriction. With intramuscular cortisone therapy there was a fall in blood pressure to normal levels concomitant with a decrease in urinary 17-ketosteroid excretion from 53 mg. per day to an average of 4.5 mg. per day. She has subsequently been maintained on cortisone at a dose level sufficient to reduce the 17-ketosteroid excretion to below 4.0 mg. per day and the blood pressure has remained normal for over two years.

The second patient was the 16½ year old sister of the first patient. An initial trial of intramuscular

cortisone induced a reduction in blood pressure and 17-ketosteroid excretion. Replacement with oral cortisone resulted in maintenance of some of the 17-ketosteroid suppression but the blood pressure returned to its initial high level, and reinstitution of intramuscular cortisone was without effect on the blood pressure until sodium was restricted in the diet despite a marked reduction of 17-ketosteroid excretion.

The third patient was a male infant with adrenal hyperplasia, first seen at the age of 20 months with hypertension and cardiac decompensation. At that time the left adrenal was removed following exploratory laparotomy. Subsequent studies on the patient showed no increase in the hypertension following the administration of desoxycorticosterone-glucoside, estradiol benzoate, or adrenocorticotropic hormone. An initial trial of cortisone intramuscularly at a dose of 50 mg. daily resulted in a drop of 17-ketosteroid excretion to near normal levels, but the patient became manic and the blood pressure rose, so the drug was discontinued. Nine months later, at which time he was moribund with signs of cardiac failure and peripheral vascular collapse, intramuscular cortisone was given in a dose of 12.5 mg. daily with a dramatic improvement in his cardiovascular condition, although he later developed a cerebrovascular accident. Subsequent maintenance on intramuscular cortisone has resulted in normal blood pressure levels and a marked decrease in cardiac size

During the patient's early course he had one hypoglycemic episode, with a blood sugar of 18 mg. per cent, suggesting a deficiency of glycogenetic adrenal hormones, which subsequent tests seemed to confirm.

CORTELL

Johnson, R. P., and Johnson, E. E.: Congenital Pulmonic Stenosis with Open Foramen Ovale in Infancy. Am. Heart J. **44:** 344 (Sept.), 1952.

Five cases of congenital valvular pulmonic stenosis with open formamen ovale occurring in infant girls (3, 4, 9, 12 and 19 months) and proved by autopsy are reported.

The syndrome includes early cyanosis, often present at birth, which may clear for a short time only to return. Dyspnea occurs in paroxysms. The heart is enlarged and a precordial systolic murmur of slight to loud intensity is present. There is clubbing of the fingers and toes. Polycythemia is present. The roentgenogram shows an enlarged heart with an upturned apex, a dilated pulmonary artery, and avascularity of the peripheral lung fields. The electrocardiogram shows marked right ventricular hypertrophy and the P waves are prominent in lead III.

Congenital pulmonic stenosis with open foramen ovale is to be differentiated mainly from pure pulmonic stenosis and from tetralogy of Fallot. In the former, cyanosis, clubbing of the digits, and polycythemia are absent. In the latter, the heart usually remains normal in size and it has a characteristic shape showing a concavity of the pulmonary artery segment. Also on cardiac catheterization the right ventricular systolic pressure is usually not as great.

A few patients with congenital pulmonic stenosis and open foramen ovale have lived to adulthood. However, when the disease manifests itself in infancy, it is a serious and treacherous disease, especially because paroxysmal dyspnea may lead to sudden death. The common "blue baby" operations of Blalock or Potts are not beneficial in pulmonic stenosis with open foramen ovale. The direct approach through the right ventricle with cutting of the stenosed valve is the procedure of choice. Indications for surgical intervention include (1) progressive heart enlargement, (2) progressive electrocardiographic changes, (3) pressure in the right ventricle of 150 mm. Hg or greater, (4) paroxysms of dyspnea, and (5) systemic arterial oxygen saturation less than 20 per cent.

RINZLER

Lequime, J., Courtoy, P., Denolin, H., and Kenis, H.: The Circulatory Dynamics of Isolated Interventricular Communications. Cardiologia **21:** 529 (Fasc. 4/5), 1952.

Four cases of isolated ventricular septal defects are reported including clinical, roentgenologic, electrocardiographic and hemodynamic data. From the pathophysiologic standpoint these congenital malformations can be divided into two main types. In the first type, with a small arteriovenous shunt, the heart is not, or is slightly, enlarged, and the electrocardiogram as well as right ventricular and pulmonary arterial pressures are normal. In the second type, in which a large arteriovenous shunt can be demonstrated, the pressure in the right ventricle and pulmonary artery is usually normal, but the right ventricular output is markedly increased. At x-ray examination the right heart is hypertrophic, the pulmonary arteries dilated and the electrocardiogram shows marked right axis deviation and frequently some degree of intraventricular or atrioventricular block. It is concluded, that the clinical aspects and the prognosis of an interventricular septal defect depend entirely on the degree and dynamic importance of the arteriovenous shunt present in this type of congenital malformation.

PICK

CONGESTIVE HEART FAILURE

Cournand, André: A Discussion of the Concept of Cardiac Failure in the Light of Recent Physiologic Studies in Man. Ann. Int. Med. **37:** 649 (Oct.), 1952.

Hemodynamically, cardiac failure is best defined as a state in which there is reduction of the contractile power of the ventricular muscle in the face of an increasing filling pressure. According to Starling's

experiments, this reduction occurs when the fibers are stretched beyond a critical point. The intimate cause of the mechanical inefficiency of the muscular fibers developing beyond this critical point seems to reside, in most instances, not in a reduced supply of oxidative energy, but in the inability of the fibers to transform this oxidative energy into useful work, as a result of ineffective biochemical processes involving carbohydrate metabolism and the specific contractile proteins. Be that as it may, the reduction in contractile power is essentially the result either of a primary alteration of the myocardial fibers or of an overloading of the venous return associated with hypervolemia. Both factors may be present singly or combined in various proportions, according to the nature of cardiac lesions and the stage of evolution of cardiac failure. In any event, a relative reduction in cardiac output and the associated increase in the end diastolic filling pressure, and therefore in the volume of blood left in the ventricle at the end of systolic ejection, are the hemodynamic earmarks of the failure of the ventricular pump. Indeed, the output of the failing heart at rest, under basal metabolic conditions, is not necessarily less than that of a normal heart in the same state: the reduction in output is not always absolute, but it is relative to that existing immediately preceding the onset or following the relief of failure—other variables, notably the blood volume, remaining the same. The homeostatic mechanism whereby the aortic pressure remains constant in the face of a reduction in cardiac output leads to the maintenance of an adequate perfusion pressure into the coronary circulation; but since the prolongation of the reflex mechanism causes a persistent reduction of the renal blood flow, it may be considered to be a source of embarrassment to the heart by eventually promoting hypervolemia, and thereby increasing the circulatory load. Physiologic studies in man indicate that in patients with left ventricular failure the administration of digitalis is followed by a rapid fall of all pressures in the pulmonary artery, an increase in cardiac output and stroke volume, a slight rise of the systolic and pulse pressure in the systemic artery, the end diastolic pressure in the right ventricle remaining unchanged. In cases of right ventricular failure associated with a considerable increase in total blood volume and increased cardiac output, measurements made after digitalis therapy demonstrate a rise in cardiac output and stroke volume, a return of the end diastolic pressure in the right ventricle to a normal level, without any significant variation of the mean pressure in the pulmonary artery. The latter finding is ascribed to absence of any change in left ventricular filling pressure since the left ventricle had not been in failure. In the same type of case, after the blood volume was reduced following a series of repeated phlebotomies, the results of physiologic studies were similar to those obtained after digitalization. The similar response is ascribed to the improved myocardial contractility of the failing right ventricle, which follows either digitalization or phlebotomy.

WENDKOS

Stapleton, J. F., and Harvey, W. P.: Hypochloremic Alkalosis Induced by Mercurial Diuretics in Congestive Heart Failure. Arch. Int. Med. **90:** 425 (Oct.), 1952.

The development of refractoriness to mercurial diuretics often presages an unmanageable downhill course in patients with congestive heart failure. This refractory state at times is due to a disturbance of electrolyte balance. The disturbance may take several forms. The two most clearly defined types are the low salt syndrome and the hypochloremic alkalosis syndrome. The latter syndrome is emphasized as a frequent but not well-publicized complication of the use of mercurial diuretics. The relative ease of diagnosis and treatment makes its consideration mandatory in every case of refractory heart failure.

The duration of intensive ammonium chloride therapy to elevate the serum chloride depends upon the degree of depletion. Usually several days to one week is sufficient, although longer periods may be required. It is important to stress that mercurial injections should not be given during this time in order to facilitate replenishing of the chloride stores.

BERNSTEIN

Danowski, T. S.: Electrolytes and Congestive Failure. Ann. Int. Med. **37:** 453 (Sept.), 1952.

The variety of adjustments which contrive to maintain body water and electrolyte stores at a constant level no longer normally operate in congestive failure. The increases in body sodium, chloride and water which constitute the edema of congestive failure must be based ultimately on an undue retention of these constituents as taken in the diet. Because of their complexity, the etiologic and contributory factors which produce such positive balances of body water and electrolytes need to be considered separately. In regard to the venous pressure it is evident that it is usually elevated in congestive failure, irrespective of the mechanisms whereby this is mediated. This finding has a bearing upon Starling's observations relevant to the hydrostatic pressure and transudation of fluid in both the lesser and the greater circulations, though of course it need not account for all of the manifestations of congestive failure. It is also clear that increases in venous pressure are links in a chain of events which serves to augment stroke volume, that beyond a certain point this compensatory mechanism is no longer operative, and that measures such as tourniquet application, bleeding, sodium restriction, sodium, chloride and water diuresis, and digitalis administration tend to restore circulatory efficiency. The observation of Starr that venous pressure remained elevated in cardiac failure patients postmortem, led him to suggest that the plasma volume

was unduly expanded in congestive failure in relative or in absolute terms, and that its etiology must be sought in extracardiac factors. Since the kidney is the chief pathway for removal of excesses of most electrolytes, it is logical to consider the behavior of this organ in congestive failure. Virtually all studies of renal circulation during congestive failure have revealed a disproportionate decrease in the flow of blood or plasma through the kidney. This is accompanied, aggravated or produced by an increase in the vascular resistance of the kidneys. The positive balance of sodium is attributed to tubular reabsorption of sodium at an inflexible and relatively high rate, even though the sodium load is reduced. This in turn decreases the amount of sodium available for urinary excretion and leads to formation or perpetuation of edema. Furthermore, the demonstration that elevation of renal vein pressure in the dog produces a marked decrease in sodium excretion without alteration in blood flow or in filtration rate has been taken to indicate that intermittent rises in venous pressure, such as those known to occur in clinical or experimental congestion, might account for undue sodium retention in cardiac decompensation. The mechanisms through which the change in sodium loss is mediated remain obscure. There is also the possibility that increases in or increased responsiveness to adrenal cortical steroids promote sodium reabsorption in congestive failure. Hormonal or humoral changes other than those involving the adrenal steroids have been postulated to play a role in influencing renal circulation and function. Thus renin which has been demonstrated to be present in the blood of a few patients with congestive failure, may account for the efferent arteriolar constriction. VDM, found in increased concentrations in the hepatic vein of decompensated patients, has a marked antidiuretic activity. Other workers have also demonstrated or suggested the presence of unidentified antidiuretic substances in such patients. Careful studies have been reported which suggest that individuals with congestive failure have cells that are swollen as a consequence, in part at least, of increased osmotic activity of the cell base. This change may be present in the face of decreases in cell potassium with or without increases in cell sodium. With recompensation, diuresis of cell and extracellular water occurs, with a movement of potassium into cells and a decrease in the osmotic activity of cell base. Therefore, it may well be that the beneficial effects of sodium restriction on the course of vascular and myocardial disease, and the sometimes aggravating effects of sodium ingestion, are mediated through cell changes.

WENDKOS

CORONARY ARTERY DISEASE

Morrison, L. M., and Gonzalez, W. F.: The Relationship of Chronic Peptic Ulcer to Coronary Thrombosis. Am. J. M. Sc. **224:** 314 (Sept.), 1952.

The records of chronic peptic ulcer patients were examined to determine the incidence of myocardial infarction due to coronary thrombosis. A similar search was made into the records of patients with acute illnesses and chronic illnesses resulting in death. In the ulcer group, 24 per cent of 86 males (mean age, 57 years) and 20 per cent of 30 females (mean age, 59 years) had evidence of previous myocardial infarctions at autopsy. In these cases, death was caused by some complication of the ulcer. In the group dying of an acute illness, 12 per cent of 43 males (mean age, 50 years) and 4 per cent of 25 females (mean age, 52 years) had autopsy evidence of myocardial infarction. In the chronic illness group, 11 per cent of 89 males (mean age, 50 years) and 11 per cent of 63 females (mean age, 51 years) had concomitant myocardial infarction.

The authors state that the incidence of coronary thrombosis is significantly increased in patients who died from the complications of peptic ulcer. Previous work suggests that the mechanism involved may be the existence of a gastrovagal reflex producing coronary artery spasm in human subjects. Chronic peptic ulcer may produce changes in the coronary vessels through the vagus nerves according to this concept. Other factors involved may be the use of milk and cream diets leading to a rise of serum cholesterol and lipids, or a basic psychosomatic disorder which may influence both the coronary vessels and the stomach.

SHUMAN

Frisch, R. A., Kaufman, K. K., Beezy, R., and Garry, M. W.: Evaluation of Paveril in Angina Pectoris. Am. J. M. Sc. **224:** 304 (Sept.), 1952.

A group of 13 patients was selected in whom the diagnosis of angina pectoris had been established by the presence of typical symptoms, response to the Master exercise test or history of previous infarction. Subjective evaluation of placebo and Paveril-treated periods was based on the Daily Report Card Method; objective evaluation was made by the Flicker-Photometer and by the response to exercise tests.

The patients did not receive any more subjective benefit from Paveril phosphate than from placebo therapy. The objective measurements revealed that Paveril produced retinal arteriolar dilatation but did not significantly alter the response to the exercise tests. It was concluded that the dosage of 200 mg. of Paveril used in the present study was of no value in the treatment of angina pectoris.

SHUMAN

Hellerstein, H. K., Brofman, B. L., and Caskey, W. H.: Shock Accompanying Myocardial Infarction: Treatment with Pressor Amines. Am. Heart J. **44:** 407 (Sept.), 1952.

Pressor amines were administered to 18 patients in shock accompanying myocardial infarction. Shock was considered to exist in those patients who sustained hypotension (below 90 mm. Hg in previously

normotensive patients) for more than one hour and during this time exhibited classic signs and symptoms of circulatory collapse, namely, rapid pulse (sinus tachycardia) small pulse pressure, pallid cyanosis, anxiety, thirst, faintness, cold moist skin, and stupor or coma. Seventeen patients were treated with mephentermine (three also received ephedrine), and one received ephedrine alone. The series consisted of 10 women and 8 men of ages 47 to 89 years with an average of 69 years. Mephentermine was administered intravenously in 5 to 20 mg. doses or by slow intravenous drip of approximately 1 mg. per minute until a sufficient pressor response was produced. In a few cases, the intramuscular route was used, usually in 35 mg. doses. Generally repeated administration of the pressor drug was necessary over a period of 1 to 10 hours before the blood pressure was maintained. The level sought was 100 mg. Hg.

A pressor response was produced in 16 patients. Fourteen emerged from the shock state with clinical improvement for more than two days. However, seven succumbed to secondary complications 2 to 26 days later. Seven patients recovered sufficiently to be discharged from the hospital. Pressor therapy did not produce congestive failure in patients not previously in failure, nor did it aggravate pre-existing failure.

RINZLER

Turner, W. D., and Morton, V. B.: The Anoxaemic Test for Coronary Insufficiency. Brit. Heart J. **14:** 514 (Oct.), 1952.

The electrocardiographic effects of the anoxemic test were studied in 22 controls and 33 individuals who were known to have or later diagnosed as having angina pectoris or myocardial infarction. Fourteen of the patients developed abnormal electrocardiographic signs and 11 developed precordial pain. The greatest abnormality occurred in a lead overlying the left ventricle.

The authors suggest that an ST depression of 2 mm. or more in lead IV indicates a positive test and that other leads may be unnecessary.

SOLOFF

Boas, E. P., and Adlersberg, D.: Genetic Studies on Coronary Atherosclerosis Developing After the Age of Sixty Years. Arch. Int. Med. **90:** 347 (Sept.), 1952.

This study is concerned with a group of 100 unselected patients with coronary artery disease whose symptoms began after the age of 60 years. The average serum cholesterol level of these patients was 279 mg. per 100 ml. by the Schoenheimer-Sperry method. It was lower than in a previously studied group of patients whose symptoms of coronary artery disease had started before the age of 50. Among the older group fewer were hypercholesteremic. This is significant because in normal men the mean serum cholesterol level is almost identical at ages 45 and 65 (235.5 mg. per 100 ml. at 45, and 236.7 mg. per 100 ml. at 65).

Familial studies of older patients are difficult, and only 28 families of the 100 probands could be partially examined. Of the 52 siblings studied, 25 showed serum cholesterol levels of more than 280 mg. per 100 ml. The frequency distribution of serum cholesterol levels of the probands and of their siblings showed a striking parallelism. The variation of serum cholesterol level with age was also seen in the siblings. This was evident, although the readings tended to be higher than those for normal persons. This study suggests that the derangement of lipid metabolism of patients whose coronary artery disease becomes manifest after the age of 60 represents a more indolent metabolic disturbance than that encountered in the younger patients affected with this disease. However, the incidence of hypercholesteremia among the sibs of the older group does not differ significantly from that among the sibs of the younger group.

BERNSTEIN

Tewell, H. E., Jr., and Pritchard, J. S.: Controlled Hypoxemia Test for Coronary Insufficiency Employing the Millikan Oximeter. Arch. Int. Med. **90:** 435 (Oct.), 1952.

Fifty patients were studied during induced hypoxemia of 70 per cent arterial oxygen saturation. In normal controls, no RS-T segment deviations greater than 0.5 mm. occurred. No flat or inverted T waves were noted.

Utilizing a controlled decrease in oxygen content and frequent electrocardiograms, one can detect abnormal responses promptly. This method appears safer than waiting 10 minutes before obtaining a record. During such a period pronounced electrocardiographic changes may have developed and been allowed to persist at ever decreasing blood oxygen levels. No comparison of the frequency of positive responses following exercise and controlled hypoxemia is justified from this study, although the authors feel that a larger series of cases would show little difference between the tests. The controlled hypoxemia test is an expensive and complicated procedure. The two-step test is more easily incorporated into clinical studies.

BERNSTEIN

ELECTROCARDIOGRAPHY

Pagnoni, A., and Goodwin, J. F.: The Cardiographic Diagnosis of Combined Ventricular Hypertrophy. Brit. Heart. J. **14:** 451 (Oct.), 1952.

The authors analyzed the electrocardiographic features of three groups of patients, (1) 26 with isolated right ventricular hypertrophy due to pulmonary disease, (2) 30 with isolated left ventricular hypertrophy due to hypertension, and (3) 51 with combined right and left ventricular hypertrophy due to combined aortic and mitral valvular disease or pulmonary and systemic hypertension. All cases were confirmed by autopsy.

Of the 51 in group three, only 13 had electro-

cardiographic signs of combined ventricular hypertrophy, 13 had isolated left and 10 isolated right ventricular hypertrophy, four had left bundle branch block, two right bundle branch block and eight were nonspecific and one had intraventricular block. Left ventricular hypertrophy predominated over right and electrically vertical position was intermediate between groups 1 and 2. The relative degree of ventricular hypertrophy was not linked to the cardiographic signs of hypertrophy.

The electrocardiographic features regarded as definite for combined hypertrophy are (1) extreme clockwise rotation of QRS, (2) S is larger than R in V_5, (3) R is larger than Q in aV_R, and (4) T inverted in V_1. The features regarded as probably due to combined hypertrophy are (1) left ventricular hypertrophy with a vertical heart, and (2) clockwise rotation of heart on its long axis. The etiology of the hypertrophy does not influence these results.

SOLOFF

Evans, W., and McRae, C.: The Lesser Electrocardiographic Signs of Cardiac Pain. Brit. Heart J. **14:** 429 (Oct.), 1952.

The authors attempt to assess the significance of (1) the presence of a wave in the PQ period, (2) notching of the QRS complex, (3) an R wave immediately following an S wave, (4) depression of ST segment, (5) low, blunt or terminally dipping T wave, and (6) inverted U wave by comparing their incidence in 156 tracings of normal individuals with that of those subsequently recognized as having cardiac infarction or coronary anoxemia.

Of these (1) notching on the down stroke of $QRScr_7$ and less often $QRScr_4$, (2) depression of ST segment, (3) low Tcr_7, blunt cr_4or_7 and terminally dipping T, and (4) inversion of U are regarded as lesser signs of coronary insufficiency.

These signs are important because the mortality in this group was no lower than that with major signs.

SOLOFF

Mounsey, J. P. D., Ritzmann, L. W., and Selverstone, N. J.: Cardiographic Studies in Severe Pulmonary Emphysema. Brit. Heart J. **14:** 442, 1952.

The electrocardiographic features were analyzed in 16 instances of severe emphysema and related to right ventricular pressures.

Only two had electrocardiographic signs of right ventricular hypertrophy. One had complete right bundle branch block. Four had RSR complexes in the right precordial leads. Systemic hypertension increases the voltage of R in the left precordial leads. Nine had no electrocardiographic evidence of right ventricular hypertrophy. Congestive failure anticipated the development of cardiographic evidence of right ventricular hypertrophy in 5 of 10 instances.

The electrocardiographic features are therefore late phenomena that confirm rather than diagnose the nature of the heart disease present.

SOLOFF

Bengtson, E.: The Esophagus Electrocardiogram in Children. Cardiologia **21:** 140 (Fasc. 3), 1952.

The author recorded in 20 normal children between the ages of 1 and 12 years and in 32 children with congenital heart disease or myocarditis, multiple esophageal leads in addition to the conventional 12 leads.

At subdiaphragmatic levels, the ventricular complex had a left ventricular pattern (qR) when the anatomic and electrical axes were vertical and shifted to the right. If the axes pointed to the left and in horizontal direction the pattern was a right ventricular one (rS). The P wave in esophageal leads of normals varied in size between 2 and 6 mm. and its "intrinsic" deflection occurred within 0.04 second. P waves larger than 6 mm. were seen mainly in congenital heart disease but also in some instances of clinically diagnosed myocarditis. Prolongation of auricular activation time occurred equally in both conditions. In some cases in whom the presence of left ventricular hypertrophy was suggested on clinical grounds but not brought out by the usual leads, a strain pattern became evident in low esophageal leads or in leads from the stomach.

PICK

Andersson, T.: Electrokymographic Studies of the Left Auricular Movements in Mitral Stenosis and Insufficiency. Acta radiol. **38:** 81 (Aug.), 1952.

The author discusses his experiences with 90 patients with mitral valvular disease, studied by electrokymography. In certain instances the left auricle (auricular appendage) showed more striking changes, in others the posterior portions of the left auricle were more diagnostic.

In *mitral stenosis* the characteristic changes were (a) increased amplitude of auricular contraction curve (inward movement), evident both in increased amplitude as well as in duration of the contraction wave, (b) either a diminution in the normally falling curve during diastole, or an actual plateau-like curve, consequent to the difficulties in atrial emptying because of the obstruction, and (c) an abrupt rise in the portion of the atrial curve during the latter part of ventricular systole, presumably the release in tension within an overdistended pulmonary venous system.

In *mitral insufficiency* the characteristic findings were (a) a rise in the curve during ventricular systole, including the period preceding ventricular ejection, that is during the period of ventricular isometric contraction, and (b) a plateau type of curve in the latter part of systole.

When auricular fibrillation was present there obviously could be no auricular systolic curves character-

istic of mitral stenosis, but mitral insufficiency patterns were just as evident as in patients with sinus rhythm. In patients with pure mitral stenosis and auricular fibrillation with a rapid ventricular rate a false pattern resembling that of insufficiency could be inscribed, attributed to the altered position and relationships of the mitral valve, chordae tendineae and papillary muscles.

SCHWEDEL

Whipple, G. H.: A Simple Technique for Registering the Direction of Rotation of Vectorcardiographic Loops. Am. Heart J. **44:** 384 (Sept.), 1952.

A technic is described for recording the direction of rotation of vectorcardiographic loops through the use of a timing signal of asymmetrical wave form. An "imperfect square-wave" oscillator of electron tube type is used. This oscillator puts out an asymmetric signal whose shape varies slightly with the frequency selected and allows a choice of frequency with adequate voltage output from about 35 to over 4,000 cycles per second. The voltage output of the oscillator and the beam-intensity of the oscilloscope can be adjusted so that the sloping part of the oscillator signal will be at the correct voltage to modulate the intensity of the electron beam. This allows for an increase in the width of the tracing and therefore segmented QRS loops in which each segment will resemble a comet or a teardrop can be produced. The tails of the comets or teardrops point in the direction of the QRS loop rotation.

RINZLER

Doumer, R.: The Significance of the Point Zero in Electrocardiography. Arch. mal. coeur **45:** 1037 (Nov.), 1952.

The author presents a critical analysis of methods used by various authors for the determination of the zero point of the vectorcardiogram and the electrical center of the heart. His conclusions are as follows.

Construction of the location of the zero point from the frontal leads under application of Einthoven concept is inaccurate. With this method the incorrect assumption is made that the actual variations of electrical potential take place in a central electrical source equidistant from the electrodes. Even in experiments devised according to this principle it can be shown the variations of peripheral potentials do not correspond to the variations in the electric source. A second method attempts to determine a fixed central point at the intersection of lines which connect mirror image potentials at a certain level of the thorax. This method does not take into account irregularities of the potential lines and of the electrical field resulting from the eccentric position of the heart in the thorax and the inhomogeneity of the conductor surrounding it. Thus, in some instances the zero point constructed by this method can be shown to be situated posteriorly and/or inferiorly of the roentgenologic heart shadow.

PICK

Brink, A. J., and Goodwin, J. F.: Precordial T Deflection of the Electrocardiogram. Brit. Heart J. **14:** 331 (July), 1952.

Cooling of the precordium for 40 minutes causes the terminal portion of the T wave in the cooled region to become negative. Restoration of positivity follows the same direction. It is believed that these findings indicate that the region producing this change lies in the superficial subepicardial region.

An interpretation is made of the T wave changes in "mild" infarction, digitalis, children, adult negro, the Bantu and ventricular hypertrophy in the light of these findings.

SOLOFF

HYPERTENSION

Moyer, J. H., Huggins, R. A., Handley, A., and Mills, L. C.: Effect of Hexamethonium Chloride on Cardiovascular and Renal Hemodynamics and on Electrolyte Excretion. J. Pharmacol. & Exper. Therap. **106:** 157 (Oct.), 1952.

The effect of intravenously administered hexamethonium chloride was studied in dogs. Within two minutes of the administration of the drug, there was a marked fall in mean blood pressure due to a rapid decrease in peripheral vascular resistance. An initial increase in cardiac output was found but in most of the dogs it declined gradually and at 30 minutes was below the control value. At this period the peripheral resistance had returned almost to the control value, but hypotension persisted. In others, the hypotensive effect persisted despite a normal or slightly elevated cardiac output. The renal effects consisted of no change or slight decrease in the glomerular filtration rate and tubular function (TmG) and a reduction of the renal vascular resistance and renal blood flow. There was no definite relationship between cardiac output and renal dynamics.

The change in renal blood flow after hexamethonium chloride appears to be due to the fall in blood pressure and the decrease in renal vascular resistance without a decrease in the number of active nephrons. The hypotensive effect produced by hexamethonium can be quickly reversed by norepinephrine and epinephrine with the same kidney response that is seen in the normal intact animal.

SAGALL

Weiss, E., English, O. S., Fischer, H. K., Kleinbart, M., and Zatuchni, J.: The Emotional Problems of High Blood Pressure. Ann. Int. Med. **37:** 677 (Oct.), 1952.

The symptoms of hypertension usually arise in a social setting of emotional stress. Hence, one must

always question their relation to the high blood pressure itself, and make an effort to understand them from the viewpoint of behavior. With the discovery of the hypertension, the "blood pressure phobia" begins and often dominates the clinical picture; the new symptoms are only an exaggeration of the premorbid personality trends. These symptoms respond readily to psychotherapy, but we have no evidence that the course of hypertensive vascular disease can be influenced by psychotherapy, no matter how intensive or prolonged. Therefore, while hypertension in itself is not an indication for psychotherapy, the emotional problems that occur in association with hypertension are; and because they are so common, psychotherapy is indicated in the great majority of patients with hypertension. Such psychotherapy does not preclude medical and surgical treatment of the hypertension. Hypertension occurs in all types of personalities, from normal to psychotic, but there is a great preponderance of neurotic personalities with strong compulsive trends. Specific personality conflicts or a specific personality structure are unrelated to the hypertension. Repressed hostility is not peculiar to hypertension, as opposed to other psychosomatic disorders. It would appear that the hypertensive predisposition and the personality fault are parallel disturbances, the one inherited and exhibited in the somatic sphere, the other manifesting itself in the emotional life through thoughts and feelings. When the life situation becomes sufficiently disturbing for the particular personality, the hypertension may appear as one aspect of the personality decompensation. Having appeared, it usually pursues an irrevocable course. Failure to deal adequately with hypertension stems in large part from our failure to recognize the emotional origin of most of the symptoms that are attributed to the high blood pressure.

WENDKOS

Hoobler, S. W., Corley, R. W., Kabza, T. G., and Loyke, H. F.: Treatment of Hypertension with Oral Protoveratrine. Ann. Int. Med. **37:** 465 (Sept.), 1952.

Orally administered protoveratrine, a purified derivative of *Veratrum album*, is useful in the long-term treatment of patients with severe hypertension of diverse etiology. The drug is superior to derivatives of *Veratrum viride*, which produce, in the authors' experience, too frequent emetic side effects to be satisfactory for the long-term management of hypertensive patients. Evidence is presented that the hypotensive action of the drug is particularly useful in the treatment of left ventricular failure. Restoration of vision in malignant hypertension and relief of hypertensive headaches and encephalopathy are also notable beneficial effects. It is emphasized that the management of the hypertensive patient with protoveratrine is palliative rather than curative and that its field of particular usefulness is in alleviating symptoms and lowering blood pressure in patients in whom surgical or dietary treatment is unsuccessful or inapplicable.

WENDKOS

Bannon, W. G.: A New Sympatholytic and Adrenolytic Drug. Clinical Studies on Essential Hypertension. Proc. Staff Meet., Mayo Clinic. **27:** 475 (Nov.), 1952.

A new drug, 688-A, N-phenoxyisopropyl-N-benzyl-betachlorethylamine hydrochloride, now manufactured under the trade name Dibenzyline, is a potent sympatholytic and adrenolytic drug. It has been administered intravenously to 13 patients and orally to 15 patients with essential hypertension. The intravenous injection of 688-A causes pronounced and prolonged reduction of blood pressure of many patients with essential hypertension; orthostatic hypotension is ordinarily marked. The oral administration of 688-A in the treatment of essential hypertension needs further study. Experience with the drug has not been very impressive.

Although no alarming side effects were noted from the intravenous injection of 688-A except in one patient with essential hypertension and none from oral administration in cases of the same type, experience does not permit the author to state that 688-A will not produce serious alarming side effects if used in a larger series or for longer periods.

SIMON

PATHOLOGIC PHYSIOLOGY

Remington, J. W., Remington, R. E., and Caddell, H. M.: Production of Circulatory Failure by Electrolyte Depletion. Am. J. Physiol. **170:** 564 (Sept.), 1952.

Intraperitoneal injection of 100 to 150 ml. per kilogram of 5 per cent glucose produced a fatal circulatory collapse while 50 ml. per kilogram did not do so. The characteristics of this condition were a relatively high arterial blood pressure, very low cardiac output, high resistance and central depression. Blood volume was reduced 15 per cent. It was shown that intraperitoneal hypertonic solutions of sodium chloride produce fatal shock by dehydration accompanied by a 35 per cent reduction of blood volume. Air intraperitoneally or 200 ml. per kilogram of isotonic solution in the same area do not produce shock and rule out the factor of increased intraperitoneal pressure. This last was true although normal saline did decrease blood volume as much as intraperitoneal glucose. Plasma protein increased slightly with isotonic glucose but decreased with hypertonic solution and isotonic saline.

OPPENHEIMER

Sarnoff, S. J., and Berglund, E.: Neurohemodynamics of Pulmonary Edema. IV. Effect of Systemic Vasoconstriction and Subsequent Vaso-

dilation on Flow and Pressures in Systemic and Pulmonary Vascular Beds. Am. J. Physiol. **170:** 588 (Sept.), 1952.

Under morphine–chloralose–urethane anesthesia medullary centers were stimulated by intracisternal injection of thrombin and fibrinogen. Systemic and pulmonary arterial and venous pressures, peripheral vascular resistance were increased. In dogs in which peripheral vascular resistance rose a little over 100 per cent flow was decreased 25 per cent. In those animals having a 66 per cent increase in resistance blood flow increased 11 per cent. Atrial pressure was increased in both groups. Partial ganglionic blockade after thrombin and fibrinogen lowered peripheral vascular resistance and left atrial pressure but increased systemic flow. Phlebotomy after these same two agents lowered left atrial pressure and decreased systemic flow. Work of the ventricle is increased 48 per cent after intracisternal thrombin and fibrinogen, and decreased (25 per cent) after partial ganglionic blockade. It is emphasized that both systemic vasoconstriction and a shift of blood to lungs are needed to markedly elevate pulmonary capillary pressures. Peripheral vasodilation will prevent increases in lung volume and hence tend to offset any tendency to increase pulmonary capillary pressure.

OPPENHEIMER

Ehrenfeld, E., and De Vries, A.: Recurrent Evolution of an Acute Infarct Pattern following Attacks of Ventricular Tachycardia. Cardiologia **21:** 164 (Fasc. 3), 1952.

A case is reported of a 45 year old man who, following anterior wall infarction with typical electrocardiographic evolution, developed a tendency to protracted paroxysmal tachycardia. Two of these attacks recurring within three months were followed electrocardiographically before and following interruption by Pronestyl. On both occasions the patient developed congestive heart failure, hypotension but no chest pain. However, the electrocardiogram following conversion to sinus rhythm, revealed on both occasions the typical pattern of recent anterior wall infarction, with gradual return over several weeks to the preexistent chronic pattern.

The authors rule out the possibility of repeated recent myocardial infarction subsequent to bouts of tachycardia and explain the observed electrocardiographic alterations as "related to a change in repolarization leading to a pattern distinct from that of the usual post-tachycardia syndrome because of previous damage in the anterior wall."

PICK

Masini, V., Testoni, F., and Farulla, A.: "Focal Blocks" of the Right Intraventricular Conduction: Morphology, Pathogenesis and Clinical Significance. Cardiologia **21:** 171 (Fasc. 3), 1952.

A study was undertaken of 68 patients with alterations of the right sided precordial leads consisting in widening and notching and/or an rSr′ contour. In 80 per cent of the cases there were no significant changes in the other leads; in the remaining 20 per cent evidence of impaired intraventricular conduction was found especially in leads I, V_R and left precordial leads, and the entire tracing had the characteristics of the S-type as described by Wilson.

The focal type of right sided intraventricular blocks, with electrocardiographic abnormalities limited to part of the precordial leads, appears to be due to a conduction defect in a circumscribed area in the right ventricle. The fact that in some instances there is progression to the pattern typical for complete right bundle branch block is in support of the concept that the latter can be due to a conduction defect in the free wall of the right ventricle.

About half of the persons with focal right bundle branch block had no clinical evidence of heart disease, and in the other half mitral lesions and congenital or arteriosclerotic heart disease were present. It seems that this electrocardiographic anomaly if found in clinically healthy persons has no prognostic significance.

PICK

Herrod, C. E., Lee, R. H., Goggans, W. H., McCombs, R. K., and Gerbode, F.: Control of Heart Action by Repetitive Electrical Stimuli. Ann. Surg. **136:** 510 (Sept.), 1952.

The authors described an electronic device capable of delivering defibrillating shocks or repetitive electrical stimuli for pacemaking. This was tested on normal dogs.

Repetitive electrical stimuli in small current intensities of 2 to 3 volts and stimulus durations of from 0.02 to 0.10 second were found to be capable of superimposing beats upon the normally beating heart. They were also able to dominate the existing rhythm when the conductivity of the cardiac mechanism was altered by large doses of procaine amide. Stimuli of greater intensity or longer duration produced ventricular fibrillation.

Repetitive electrical stimuli were ineffective in the case of the heart in which the conductivity or the contractility had been damaged by anoxia, as occurred in standstill after asphyxia, in standstill following defibrillation, and in severe depression due to drugs. However, when this state did not exist, the application of the stimuli caused prompt resumption of vigorous ventricular contractions.

It was concluded that the possible clinical applications of a repetitive electrical stimulating device was still extremely limited.

ABRAMSON

Robertson, E. S., and Mathews, E. C.: Paroxysmal Ventricular Fibrillation Producing Adams-Stokes Syndrome. Arch. Int. Med. **90:** 320 (Sept.), 1952.

A case is described of paroxysmal ventricular

fibrillation producing Adams-Stokes seizures which illustrates the following: (a) the importance of establishing the underlying mechanism of Adams-Stokes attacks; (b) the association of ventricular standstill with ventricular fibrillation in the production of Adams-Stokes attacks; and (c) the potential aggravating effect of quinidine in ventricular fibrillation, especially in the presence of complete heart block and intraventricular block.

Paroxysmal ventricular fibrillation occurs most frequently in persons with serious heart disease, chiefly with atrioventricular dissociation and after coronary occlusion with myocardial infarction. However, it has been reported in several instances in persons with no demonstrable heart disease. Factors favoring ventricular fibrillation include anoxia, ischemia, intravenous administration of drugs, and toxic doses of drugs, especially digitalis and quinidine. Ventricular fibrillation also may occur in chloroform or cyclopropane anesthesia, especially when the circulating epinephrine concentration is increased by injection or anxiety.

Since, to date, there is no standard therapeutic program for the management of ventricular fibrillation, the treatment must be individualized. Drugs useful in the treatment of Adams-Stokes seizures due to ventricular standstill (including epinephrine, ephedrine, and barium chloride) probably should not be used. Among the measures which may be given consideration are the following: (a) oxygen therapy; (b) cautious administration of coronary vasodilators, such as aminophyllin and papaverine; (c) administration of procaine amide orally or cautiously intravenously; and (d) administration of sedatives, including bromides and phenobarbital.

BERNSTEIN

Bennet, I. L., Jr., and Walker, W. F.: Cardiac Arrhythmias Following the Use of Large Doses of Central Nervous System Stimulants. Am. Heart J. **44:** 428 (Sept.), 1952.

Two cases of cardiac arrhythmias in patients treated with large doses of nikethamide, caffeine, and amphetamine are reported. In the first patient 14 Gm. of caffeine and sodium benzoate, 12 Gm. of nikethamide, and 40 mg. of amphetamine intravenously produced bigeminy due to ventricular premature contractions 15 hours after administration. In the second patient, the intravenous administration of 11 Gm. of nikethamide, 11.5 Gm. of caffeine sodium benzoate, and 100 mg. of amphetamine resulted within five hours in depression of the S-T segments and a large U wave. The rhythm soon became irregular due to the appearance of ventricular premature beats and rapidly progressed to chaotic heart action. Cardiac arrest occurred three hours later despite treatment with procaine amide, calcium gluconate, and epinephrine.

RINZLER

Mann, R. H., and Burchell, H. B.: Premature Ventricular Contractions and Exercise. Proc. Staff Meet., Mayo Clinic. **27:** 383 (Sept.), 1952.

A study was made of 21 cases in which premature ventricular contractions were present in electrocardiographic tracings obtained after exercise tests. It appears that precipitation of ventricular tachycardia (or premature contractions) by exercise should suggest, but not necessarily be considered diagnostic of, the presence of cardiac disease. It is more difficult to draw definite conclusions about patients in whom premature ventricular contractions persist or become more frequent after exercise. The exercise test is a functional one, and although positive results furnish good evidence for coronary insufficiency, negative results do not exclude such a condition. With this qualification, it can be stated that those patients who displayed a persistence or an increased frequency of premature ventricular contractions after exercise most frequently did not show evidence of coronary insufficiency.

Although not specifically included in this study, a case was observed in which premature ventricular contractions were present during rest but were abolished by exercise. Coronary insufficiency was present both clinically and as evidenced by positive results of the exercise test. The fact that premature ventricular contractions are abolished by exercise does not exclude coronary insufficiency.

SIMON

Condorelli, L.: Regulatory Mechanisms of Pulmonary Arterial Pressure. Cardiologia **21:** 379 (Fasc. 4/5), 1952.

The author constructed a special apparatus for simultaneous and continuous recording of pressures in the pulmonary and femoral arteries in man and in larger experimental animals. In this way various mechanisms regulating conditions of the systemic circulation could be demonstrated to be without effect upon the pulmonary circulation. Thus a physiologic sympathetic tone appeared to be hardly of any significance in the pulmonary artery and no cholinergic nerve endings could be traced in the pulmonary arterial system.

On the basis of these experiments it is concluded that systemic and pulmonary hypertension are two entirely different entities. The latter apparently develops over some unknown proprioceptive mechanisms in the pulmonary circulation.

PICK

Wright, H. P., and Osborn, S. B.: Effect of Posture on Venous Velocity, Measured with $NaCl^{24}$. Brit. Heart J. **14:** 325 (July), 1952.

Radioactive sodium was used to study the effect of posture on the blood flow in the lower limbs. The blood flow was equal in both limbs and under standard conditions, average 4.2 cm. per second. The flow rate is about halved in the standing or sitting posi-

tion compared to that of the supine and is doubled with the head down about 10 degrees or with gentle exercise of the feet. The rate was not changed upon crossing the knees.

The authors believe that these findings are significant. They advise elevation of the foot of the bed and gentle movements of the feet postoperatively to prevent thrombosis of the veins of the lower limbs.

SOLOFF

Denney, J. L., Miller, H., Griffith, G. C., and Nathanson, M. H.: Ventricular Acceleration Following Procaine Amide Hydrochloride Therapy. J.A.M.A. **149:** 1391 (Aug. 9), 1952.

A case of ventricular tachycardia treated with intravenous procaine amide is reported, in which the following events occurred: (a) progressive and pronounced widening and notching of the QRS wave of the electrocardiogram, (b) a short paroxysm of ventricular acceleration of the prefibrillation type, and (c) restoration of sinus rhythm. The authors suggest that, as with quinidine sulfate therapy, a widening of the QRS wave during the administration of procaine amide hydrochloride may represent a precursor to ventricular fibrillation and is an indication for discontinuance of use of the drug.

KITCHELL

Pederson, A., and Warburg, E.: Starling's "Law of the Heart" Elucidated Through the Filling Pressure of the Right Ventricle in Atrial Septal Defect. Cardiologia **21:** 517 (Fasc. 4/5), 1952.

In 20 patients with definite proof of an atrial septal defect with left to right shunt, the pressures in the right auricle, right ventricle and the pulmonary capillary pressure were compared with corresponding values obtained in a control group of cases without cardiac disease.

In atrial septal defect the pulmonary blood flow increases to twice the normal and the filling pressure of the right ventricle is distinctly higher than normal. Thus the increase of stroke volume of the right ventricle appears to be a true Starling effect. However, the pressure in the pulmonary capillaries in an atrial septal defect does not differ from normal and the output of the left ventricle is definitely lowered. The latter appears to be the consequence of some secondary regulatory mechanism of unknown nature.

PICK

Guyton, A. C., and Satterfield, J. H.: Vasomotor Waves Possibly Resulting from CNS Ischemic Reflex Oscillation. Am. J. Physiol. **170:** 601 (Sept.), 1952.

Hemorrhage and elevated cerebrospinal pressure when combined will usually make the arterial pressure oscillate. The authors suggest the following mechanisms: CNS ischemia (due to elevated CSF pressure) excites the vasomotor center; mean blood pressure rises above the CSF pressure; this relieves ischemia; blood pressure then falls below CSF pressure and the cycle starts again. Pressoreceptor denervation does not prevent these waves.

OPPENHEIMER

PATHOLOGY

Pomerantz, H. Z., Darragh, J. H., and Mallory, G. K.: Recurring Dissecting Aneurysm of the Aorta. Canad. M. A. J. **67:** 339 (Oct.), 1952.

The authors report a case of recurring dissecting aneurysm of the aorta in which the original dissection occurred six months prior to death and the final dissection in the ascending aorta led to occlusion of the carotid artery with hemiplegia and terminal cardiac tamponade. Dissections which do not compromise the blood supply of major arterial trunks are compatible with long periods of survival and are at the same time the most difficult type of dissection to diagnose ante mortem.

BERNSTEIN

Kirkeby, K., and Leren, P.: Myxoma of the Heart. Polypoid Tumor of the Left Atrium Diagnosed Ante Mortem. Acta med. scandinav. **143:** 385 (Oct.), 1952.

The case of a man aged 50 years is described. The antemortem diagnosis of polyp of the left atrium was made on the basis of varying auscultatory findings over the heart. When in the erect position the murmurs suggested mitral stenosis whereas in the recumbent position they suggested mitral regurgitation. Furthermore the patient developed cardiac decompensation which displayed a rapid progression with enlargement of the liver, edema and dyspnea. Postmortem examination disclosed a hemangiofibromyxoma 5 cm. by 5 cm. by 3 cm. in size attached to the endocardium 5 cm. above the posterior commissure of the mitral valve and protruding through the mitral valve ring which appeared dilated. The symptoms and signs which are said to be suggestive of polyps of the left atrium are (1) lack of rheumatic history, (2) short history with rapid progression of decompensation when it occurs, (3) attacks of dyspnea, cyanosis, tachycardia and precordial pain, at times occurring in relation to alterations of posture permitting mass to fall into mitral orifice, (4) attacks resembling Stokes-Adams syndrome, (5) auscultatory findings which may vary with changes in position, (6) peripheral or central embolism, (7) increased sedimentation rate and fever, (8) hypotension, (9) radiographic evidence of enlargement of left atrium and right ventricle, and (10) ineffectiveness of digitalis. The possibility of surgical intervention and removal of polyps from the left atrium is discussed briefly.

ROSENBAUM

PHARMACOLOGY

Schack, J. A., Hoffman, I., and Vesell, H.: The Response of Arrhythmias and Tachycardias of

Supraventricular Origin to Oral Procaine Amide. Brit. Heart J. **14:** 465 (Oct.), 1952.

The authors report the effects of oral procaine amide upon one hundred instances of supraventricular arrhythmias or tachycardias which occurred in 83 individuals. After a test dose of 250 mg., 1 Gm. was given every four hours. If after 5 Gm., the arrhythmia had not been abolished, 1 Gm. was given every three hours.

Auricular fibrillation was abolished in 17 of 21 of less than one week duration, 15 of 25 of less than three years' duration and 3 of 15 of more than three years' duration. Auricular flutter was abolished in only one of seven instances. All nine instances of paroxysmal auricular tachycardia were abolished. Two of three instances of auricular premature contractions were controlled. All four with nodal tachycardia were readily returned to sinus rhythm.

The maintenance dose was 0.5 Gm. every six hours for two to four weeks.

The toxic effects noted were nausea, vomiting, malaise, weakness, marked diaphoresis and profound prostration.

SOLOFF

Lucas, B. G. B., and Short, D. S.: Procaine Amide in the Control of Cardiac Arrhythmias. Brit. Heart J. **14:** 470 (Oct.), 1952.

Procaine amide abolished four of five instances of ventricular tachycardia, 7 of 13 instances of ventricular premature beats, four of nine episodes of supraventricular tachycardia, two of six instances of supraventricular premature beats and three of eighteen instances of auricular fibrillation. Treatment was of limited value in prophylaxis.

In 28 individuals undergoing catheterization and 24 undergoing cardiac surgery, the drug was of no value in preventing the arrhythmia produced by mechanical trauma.

SOLOFF

Erspamer, V.: Observations on Alleged Serotonin-(Enteramine)-Like Nature of Cerebral Pressure Substance of Taylor, Page, and Corcoran. Arch. Int. Med. **90:** 505 (Oct.), 1952.

Serotonin, a circulating enteramine, is by no means a pure hypertensive agent, inasmuch as it can provoke hypertensive, hypotensive, and biphasic reactions, according to the animal species, the dose, and the conditions of the circulatory system. 1-Hydrazinophthalazine (C-5968) cannot be considered a specific inhibitor of enteramine. So far, no convincing evidence exists that the cerebral vasopressor principle of Taylor, Page, and Corcoran belongs to the series of the enteramine-like substances. Therefore, all the clinical and etiopathogenetic deductions which the authors have drawn from their hypothesis are premature.

BERNSTEIN

Kirkland, G. S., and Malach, M.: The Clinical Use of Norepinephrine in the Treatment of Shock Accompanying Myocardial Infarction and Other Conditions, New England J. Med. **247:** 383 (Sept. 11), 1952.

Norepinephrine (aminoethanol catechol) has been found to produce a generalized arterial, capillary and venous vasoconstriction with an increase in total peripheral resistance and a resultant increase in systolic, diastolic and mean systemic arterial blood pressures. There is an increase in the mean arterial, capillary and venous pressure in the pulmonary circuit. The cardiac output is decreased as is the pulse rate in the normotensive human being and the intact animal. Renal plasma flow is decreased but the filtration fraction is increased and cerebral blood flow is decreased although there is no change in cerebral oxygen consumption. Norepinephrine has neither the calorigenic nor hyperglycemic actions of epinephrine. It does not produce the anxiety, restlessness or apprehension produced by epinephrine.

Thirty patients were treated with 37 infusions of epinephrine. In 14 patients the drug was used because of shock associated with acute myocardial infarction, whereas in the remaining 16 the shock was due to a miscellany of other causes. Ampules containing 4 mg. of the drug were diluted in 1000 cc. of 5 per cent glucose or 0.85 per cent saline to yield a solution containing 4 μg. per cubic centimeter for intravenous administration. The solution was given at an average rate of 20 to 30 drops per minute, the flow usually sufficient to elevate the systolic pressure to 100 or to alleviate the clinical manifestations of shock. It was found that abrupt cessation of norepinephrine often resulted in a sudden drop of blood pressure; consequently, the rate of flow was gradually decreased over a period of four to six hours after the blood pressure became stabilized. The largest amount of the drug administered to a single patient was 62 mg. during five days. A significant pressor response occurred in 12 of 17 courses of treatment in 14 patients with shock accompanying myocardial infarction. Four of these patients ultimately survived. Aggravation of congestive failure or pulmonary edema, already present because of myocardial infarction, did not result from norepinephrine administration. A significant pressor response was observed in 18 of 20 courses of treatment in 16 patients with shock from other causes; only three of these patients ultimately survived. In this series a pressor response was obtained in many patients who had previously failed to respond to other measures including oxygen, shock blocks, plasma, whole blood, paredrine, Neosynephrine and epinephrine.

The most important complication of treatment was the appearance of local venospasm, pallor, cold skin and cyanosis in the area of insertion of the needle within 1 to 24 hours after institution of the infusion. This occurred in 14 of the 30 cases. Red streaky phlebitis and vesicular eruption or ulcera-

tion occurred in some cases. Extravascular infiltration of neoepinephrine may produce intense vasospasm with subsequent necrosis and ulceration of the skin. It is recommended that the drug be given with caution in the presence of peripheral vascular disease or diabetes mellitus.

ROSENBAUM

Lands, A. M., and Howard, J. W.: A Comparative Study of the Effects of l-Arterenol, Epinephrine and Isopropylarterenol on the Heart. J. Pharmacol. & Exper. Therap. **106:** 65 (Sept.), 1952.

The effects of varying concentrations of l-arterenol, epinephrine, and isopropylarterenol on the rate and amplitude in the perfused frog heart, the isolated tortoise sino-auricular preparation, the isolated auricle of the rabbit, and in the perfused rabbit heart were investigated. Epinephrine was found to be more effective than l-arterenol in increasing the amplitude and rate of contraction in the perfused frog heart and the tortoise isolated sino-auricular preparation but less effective in the isolated rabbit auricle and perfused rabbit heart. In the frog and tortoise heart changes in amplitude were induced more readily by both drugs than changes in the rate of contraction while the reverse was found in the rabbit heart. These differences in action suggest that the drugs act on different receptor mechanisms in producing the changes in rate and amplitude and that there are species differences in sensitivity for both effects. In regard to changes in rate and amplitude isopropylarterenol was found to be many times more potent than the other two drugs in all the four preparations studied. The three agents were found to have a critical concentration for the effects produced and wide variations of concentration on either side of this critical level did not cause significant changes in rate or amplitude of contraction. The capacity of the isolated rabbit auricle to follow on artificial pacemaker was increased frequently by relatively high concentrations of epinephrine and l-arterenol and more so by isopropylarterenol and was reduced by lower concentrations.

SAGALL

Ruben, H., and Morris, L. E.: Effect of Cocaine on Cardiac Automaticity in the Dog. J. Pharmacol. & Exper. Therap. **106:** 55 (Sept.), 1952.

The effect of intravenously administered cocaine on epinephrine-induced arrhythmias was studied in conscious and cyclopropane-anesthetized dogs. Injection of epinephrine after cocaine or the simultaneous injection of cocaine and epinephrine produced and increased cardiac effect as compared with the injection of epinephrine alone and in all experiments. The injection of cocaine alone did not induce cardiac irregularities. The authors conclude that cocaine either increases the sensitivity of the heart to epinephrine or delays the destruction of epinephrine.

SAGALL

Dearborn, E. H., and Lasagna, L.: The Antidiuretic Action of Epinephrine and Norepinephrine. J. Pharmacol. & Exper. Therap. **106:** 122 (Sept.), 1952.

Studies performed on unanesthetized dogs during a water diuresis after the intravenous administration of epinephrine or norepinephrine revealed two types of antidiuretic effects. The first was a rapid inhibition of less than ten minutes duration associated with a decrease in glomerular filtration rate and renal blood flow occurring probably as a consequence of renal vasoconstriction. The second type was a long effect persisting after the circulation had returned to a normal state. When the hypothalamo-hypophyseal system was damaged surgically, this long antidiuretic effect was not found. These studies suggest that the long antidiuretic effect is due to liberation of antidiuretic hormone from the posterior pituitary by injected epinephrine or norepinephrine.

SAGALL

Winsor, T.: Effects of Hydrogenated Alkaloids of Ergot on Vasomotor Reflexes. Am. J. M. Sc. **224:** 42 (July), 1952.

The effect of the hydrogenated alkaloids of ergot upon peripheral blood flow, skin temperature, blood pressure, venous pressure and oscillometry was measured in 69 patients with hypertensive disease and in 11 normal subjects. The ergot preparations were administered orally and intravenously and consisted of three compounds in a single tablet or solution known as CCK 179. This drug consistently caused a hypotensive effect after the injection of 1 mg. with the subject supine and occasionally after an oral dose of 3.0 mg. with the subject erect. The drug appears to be a sympathetic nervous system depressant, acting centrally, at the ganglion or peripherally. These effects are demonstrated by a decrease in peripheral resistance, accompanied by an inhibition of induced and spontaneous vasomotor activity of the digits, a decrease in sweating and a decrease in the cold pressor response after administration of the drug. The depressor effect noted was variable in the hypertensives and appears to be most marked in those with a significant neurogenic aspect to the disease. It is suggested that this drug be utilized over long periods of time to determine whether or not the hypotensive effects can be maintained.

SHUMAN

Jessar, R. A., Horwitz, O., and Montgomery, H.: The Vasodilator Effects of Intravenous Procaine in Patients with Ischemic Extremities. Am. J. M. Sc. **224:** 300 (Sept.), 1952.

The vasodilating action of intravenous procaine was evaluated in nine patients with evidence of peripheral vascular disease and ischemic extremities. Basal vascular tone and reflex vasodilatation tests were performed. The patients received 250 cc. of 0.1 or 0.2 per cent solution of procaine hydrochloride in saline

for a period of 10 to 70 minutes after a preliminary set of data were obtained using saline above. In fou patients undesirable side effects of precordial oppression, nervousness, drowsiness, light headedness or perioral numbness were noted. The administration of procaine produced no significant change in digital cutaneous blood flow, blood pressure, cardiac output, pulse rate or temperature when compared to a normal group of controls.

SHUMAN

Rosenthal, N., and Rosenthal, R. L.: Treatment of Polycythemia Vera with Triethylene Melamine. Arch. Int. Med. **90:** 379 (Sept.), 1952.

Thirty patients having polycythemia vera were treated with triethylene melamine. Twenty patients showed a satisfactory symptomatic and hematologic response, with an average remission of eight to nine months following an average course of 30 mg. of triethylene melamine. Analysis of these cases revealed that patients with a shorter duration of disease and normal thrombocyte and white blood cell counts responded more favorably to treatment than did patients with a long history of the disease and elevated white blood cell and thrombocyte counts. The additional value of triethylene melamine as a depressant of elevated thrombocyte counts is discussed in relation to thromboembolic and hemorrhagic complications.

This study indicates that triethylene melamine offers good potentialities in the treatment of polycythemia vera. Further observation is necessary before valid comparisons with this therapy can be made.

BERNSTEIN

Melville, K. T.: On the Mechanism of the Cardiovascular Actions of Digitalis; Observations on the Influence of Flaxedil, Atropine or Vagotomy. J. Pharmacol. & Exper. Therap. **106:** 208 (Oct.), 1952.

The effects of Flaxedil, atropine and vagotomy on the cardiovascular response (blood pressure, heart rate, and electrocardiographic changes) to intravenously injected ouabain and digitoxin were studied in anesthetized dogs. Flaxedil was found to block the reflex vagal control of the heart and the cardioinhibitory action of acetylcholine but to prolong the depressor response to acetylcholine and to increase the excitatory response of the heart to epinephrine. The previous injection of Flaxedil or atropine affected the cardiac and vascular responses to ouabain and digitoxin. The reflex vagal bradycardia was blocked and the usual pressor response was diminished, but an initial slowing of the heart rate followed by a sinus tachycardia appeared and the usual T-wave changes were present. Cutting of the vagi in the neck after previous injection of Flaxedil or atropine followed by ouabain or digitoxin resulted in a prompt rise in blood pressure without a significant change in the heart rate. This effect was not apparent when the vagi were sectioned in the chest below the heart or lungs. After previous double cervical vagotomy without the injection of Flaxedil or atropine, a marked sustained pressure response was induced by ouabain or digitoxin. The results suggest that ouabain and digitoxin can slow the heart by some nonvagal action apparently associated with a direct effect on the myocardium. The pressor response of digitoxin and ouabain observed after the cutting of the vagi in the neck apparently is associated with the release of some afferent reflex vasoinhibition originating in the heart itself under the influence of digitalis. This effect is similar to the "Bezold effect" and may be an important factor in the therapeutic action of digitalis in cardiac failure.

SAGALL

Best, M. M.: Management of Khellin Toxicity: Effects of Dosage and Purification. Am. J. M. Sc. **224:** 308 (Sept.), 1952.

Because of the toxicity associated with the Visnagin portion of Khellin preparations, the author employed a purified crystalline khellin product largely devoid of Visnagin to reduce the incidence of side effects commonly observed with the cruder forms. Several patients were found intolerant to the crude preparation but were able to tolerate similar dosages of purified khellin. However, toxic manifestations of gastrointestinal origin were observed with crystalline khellin the incidence of which depended upon the dosage utilized. The drug was found to be effective in reducing anginal pain and preventing abnormal electrocardiographic responses to exercise and anoxemia in doses ranging from 30 to 120 mg. per day. It is suggested that purified khellin is less toxic and may be effective in lower doses and that the minimum effective dose for each patient must be ascertained.

SHUMAN

Brofman, B. L., Hellerstein, H. K., and Caskey, W. H.: Mephentermine—An Effective Pressor Amine. Am. Heart J. **44:** 396 (Sept.), 1952.

Mephentermine (N-methylphenyl tertiary butylamine), is a new pressor substance with theoretic norepinephrine-like activity. In dogs, usually 0.3 to 0.5 mg. per kilogram administered intravenously by infusion over a 6 to 10 minute period was able to effect a rise in mean blood pressure of 10 to 30 per cent above the control level. Associated with this pressor response, the following occurred: there was little change in heart rate except for reflex slowing; pulmonary artery pressure increased slightly; no significant electrocardiographic effects occurred; oxygen consumption increased; the respiratory rate showed variable but definite increase; and the cardiac output at the height of the pressor effect showed no significant variation from control values. Coronary flow was increased even under constant

coronary perfusion pressure by slow intravenous infusion.

Mephentermine was administered to volunteer hypotensive, normotensive and hypertensive patients in graded doses of 5 mg., 10 mg., and 20 mg., and observations were recorded until the blood pressure returned to normal. Most patients received 35 mg. over a one-half hour period with a total volume of infusion not exceeding 50 cc. With these doses, there was little or no direct action upon the heart as measured by changes in rate, rhythm, and irritability. Side reactions such as cerebral stimulation, pupillary changes, blood sugar changes, respiratory stimulation, and metabolic rate increase were absent or insignificant. The cardiac output was relatively unaltered and heart work was increased in normal and hypotensive patients.

Based on these experiments, the authors outline the following dosage schedule as practical: an intravenous priming dose of 10 to 20 mg. or more, followed by an intravenous infusion of approximately 5 mg. per minute, the rate of infusion to depend on the desired blood pressure. A sustained blood pressure can be obtained by intramuscular injection of 15 to 35 mg. at one-half hour intervals, or longer.

Mephentermine then appears to be a suitable drug for use in treating acute hypotensive states, especially shock following myocardial infarction. It has proved effective in sustaining blood pressure in cardiovascular operations without producing arrhythmias.

RINZLER

Morris, L. E., Yein, C. S., Haid, B., and White, J. M., Jr.: Laboratory and Clinical Observations on the Effect of Regitine (C-7337) on Cardiac Irregularities During Cyclopropane Anesthesia. J. Pharmacol. & Exper. Therap. **106:** 48 (Sept.), 1952.

In 21 experiments made on nine dogs, the authors found that Regitine markedly reduced the incidence and severity of ventricular arrhythmias induced by epinephrine during cyclopropane anesthesia. In 58 gynecologic patients anesthetized with cyclopropane, Regitine was administered preoperatively to 23 patients either orally (60 to 120 mg. one to one and one-half hours prior to induction of anesthesia) or intravenously (0.33 mg. per kilogram body weight 10 to 15 minutes prior to induction of anesthesia). In all patients electrocardiograms were recorded prior to and at intervals during anesthesia. In addition the electrocardiographic pattern was continuously observed with an oscilloscope during the operation. No significant reduction in ventricular irregularities was observed in the Regitine premedicated group as compared with the control group. In addition the injection of Regitine during anesthesia did not reduce the incidence of ventricular irregularities.

SAGALL

PHYSICAL SIGNS

Edwards, E. A., and Levine, H. D.: Peripheral Vascular Murmurs. Arch. Int. Med. **90:** 284 (Sept.), 1952.

This is a study of murmurs generated within the peripheral blood vessels in a variety of disorders. The murmurs are presented as registered by phonocardiographic apparatus, and correlation is made with roentgen visualization of the vessels. Murmur production at an area of narrowing was studied by compression of the brachial artery in normal persons. Murmurs at, or distal to, the site of compression consist of three components: an early systolic impact, a later systolic stenotic flow, and a protodiastolic recoil. A murmur consisting of impact and recoil, with an occasional trace of the transmitted stenotic flow, is discernible proximal to the obstruction. Elevation of the pulse pressure intensifies and prolongs all three components, especially the impact.

Arterial murmurs are mainly systolic in time, owing to the existence of a high pressure gradient at this pulse phase. Elements of the three components mentioned above are noted in the murmurs heard when the lumen is narrowed, whether by external pressure as with cervical rib or in the scalenus maneuver, or in intrinsic obstruction as by arteriosclerosis. A gruff systolic murmur was heard over the aorta or over the iliac or femoral arteries in about half of all patients with arteriosclerosis. No murmurs were heard in thromboangiitis obliterans or proximal to arterial thrombosis. Arterial aneurysms often failed to give the classic systolic murmur, probably because of parietal thrombosis. The continuous murmur of arteriovenous fistula was studied. Constriction of the effluent vein converted such a murmur to a systolic one by eliminating the necessary gradient for a critical velocity in the diastolic phase. A murmur, probably due to high velocity flow, is heard far along the vein proximal to a fistula.

BERNSTEIN

Reubi, F., Vogt, H., and Plancherd, B.: Presystolic Murmur in a Case of Obliterating Pulmonary Arteritis. Cardiologia **21:** 90 (Fasc. 2), 1952.

A case is described of a 57 year old patient with recurrent and progressive right heart failure. There was a distinct presystolic murmur heard over the apex which together with other clinical electrocardiographic and roentgenologic signs suggested the diagnosis of mitral stenosis. The condition responded poorly to the conventional cardiac therapy and the patient died after several months of observation.

At autopsy, a generalized panarteritis was found which involved mainly the pulmonary vascular tree, with obliteration of many small vessels. There was a marked dilatation of the main pulmonary artery associated with a relative insufficiency of the pulmonary valves. The right auricle and ventricle were hypertrophied and dilated, but there was no organic involvement of any valve. On the basis of these find-

ings the authors attribute the apical presystolic murmur to a functional tricuspid stenosis which is analogous to the mechanism implied for the explanation of an Austin-Flint murmur in the presence of aortic regurgitation.

PICK

Landulfo, J.: A Contribution to the Study of Femoral Vascular Sounds. Arq. brasil cardiol. **5:** 119 (June), 1952.

The production of femoral vascular sounds was studied in a series of 90 records which included simultaneous phonograms and phleboarteriograms. According to the author, there are four main femoral sounds which are variably combined, giving rise to double, triple or quadruple rhythms.

The presystolic sound originates in the valves of the femoral vein during the sudden increase of local venous pressure due to right auricular systole in the presence of venous stasis.

The diastolic arterial sound originates in the rapid and wide distention of the femoral artery.

A postdiastolic arterial sound follows the diastolic arterial sound. The probable pathogenesis of this acoustic element is that the diastolic distention of the femoral artery compresses the femoral vein and empties it; during the subsequent arterial systole, there is a backward venous flow which causes vibration of the valves of the femoral vein.

A late sound occurs in cases associated with venous stasis and corresponds to the V wave of the jugular phlebogram. Tracings obtained by catheterization of the superior vena cava apparently confirm this explanation.

SCHLESINGER

PHYSIOLOGY

Winbury, M. M., and Green, D. M.: Studies on the Nervous and Humoral Control of Coronary Circulation. Am. J. Physiol. **170:** 555 (Sept.), 1952.

The authors investigated the effect of nervous and humoral factors on the rate of coronary blood flow in dogs under anesthesia and with the chest open. Rate of flow was increased and coronary resistance decreased by stimulation of augmentor nerves, intracoronary injection of epinephrine, l-arterenol, acetylcholine and histamine. Cardiac output and work were increased by sympathetic stimulation, epinephrine and l-arterenol. In the case of pituitrin coronary flow rate was reduced and resistance increased though other cardiovascular factors were not changed. When the vagus was stimulated, blood pressure, heart rate and coronary flow all decreased. The authors are of the opinion that changes in coronary flow are secondary to changes in blood pressure. Tetraethylammonium bromide (TEAB) reduced or prevented the effects of preganglionic stimulation but did not alter increased flow rates produced by drugs. Acetylcholine and vagus stimulation were blocked by atropine. Increased pressure within the stomach or partial constriction of the vena cava reduced coronary flow and blood pressure. The last two effects were not prevented by atropine. Increased intrabiliary tension did not change coronary flow. These experiments did not demonstrate that autonomic nerves or their mediators can produce active coronary vasoconstriction.

OPPENHEIMER

Lewis, B. M., and Gorlin, R.: Effects of Hypoxia on Pulmonary Circulation of the Dog. Am. J. Physiol. **170:** 574 (Sept.), 1952.

In these experiments cardiac output, pulmonary and femoral arterial pressure were measured. Two series of experiments were performed, one at 10 per cent inspired oxygen and another at 2.5 to 4.7 per cent oxygen. In the first group when arterial saturation was above 55 per cent saturated the pressure gradient across the lungs and the vascular resistance were increased since cardiac output was unchanged under conditions of these experiments. In the same group, when arterial saturation was less than 55 per cent, cardiac output increased and vascular resistance decreased. It is pointed out that this last response resembles that to acute severe anoxia. In the second group of dogs (2.5 to 4.7 per cent oxygen inspired) arterial saturation was below 27 per cent and pulmonary artery pressure was increased. Pulmonary vascular resistance was decreased in most cases. At values below 15 per cent saturated left arterial pressures were increased. Cardiac output was increased in acute severe anoxia but decreased if conditions were maintained. There was no change in output with mild or localized anoxia and it is associated with pulmonary vasoconstriction. It is considered that this vasoconstriction is due to direct local action on vessels. Acute severe hypoxia increases output but decreases resistance in the pulmonary vessels.

OPPENHEIMER

Stevenson, I. P., Duncan, C. H., Flynn, J. T., and Wolf, S.: Hypertension as a Reaction Pattern to Stress. Correlation of Circulatory Hemodynamics with Changes in the Attitude and Emotional State. Am. J. M. Sc. **224:** 286 (Sept.), 1952.

A group of hypertensive patients were studied from the viewpoint of their personalities and responses to stressful life situations in correlation with symptoms and measurements of circulatory function. Among the latter observations were included cardiac output and peripheral resistance using the Nickerson-type ballistocardiograph, the Master exercise tolerance test in 20 patients and measurements of renal blood flow and glomerular filtration rates in two patients.

The exercise tolerance test during relaxation in both hypertensives and normal controls produced a slight elevation of mean blood pressure and slight lowering of peripheral resistance. Following the

discussion of stressful life situations both groups showed an increase in cardiac output, rise in blood pressure and a fall in peripheral resistance. The hypertensive patients manifested a greater rise in blood pressure especially when the reaction was characterized by restraint and resentment indicating a greater vasoconstrictor response in this group. The effect upon renal hemodynamics was to lower renal blood flow and glomerular filtration during the period of blood pressure elevation presumably because of constriction of the efferent glomerular arteriole. In sympathectomized hypertensive patients, the responses to stressful interviews was modified but not profoundly affected. When the reaction to the interview was one of defeat and resignation, a hypotensive response may be observed. However, in general, it may be stated that the hypertensive displays a greater vasoconstrictor response to stress than does the normotensive.

SHUMAN

RHEUMATIC FEVER

Biörck, G., Winblad, S., and Wulff, H. B.: Studies in Mitral Stenosis. II. Observations on Incidence of Active Rheumatic Carditis in Left Auricular Appendages Resected at Operation for Mitral Stenosis. Am. Heart J. **44:** 325 (Sept.), 1952.

The erythrocyte sedimentation rate, the blood culture, the antistreptolysin titer, and the agglutination of sensitized erythrocytes were determined on 18 patients with mitral stenosis accepted for surgical intervention in order to disclose possible rheumatic activity or subacute bacterial endocarditis. Rheumatic activity was also judged from a detailed history, physical examination, temperature chart and electrocardiogram. These 18 patients were considered to have no demonstrable active rheumatic process preoperatively and at operation the diagnosis of a mitral valvular lesion was confirmed in all instances at which time specimens of the left auricular appendage were removed for microscopic study.

From a pathologic-anatomic point of view the patient fell into four groups: (1) typical subendocardial rheumatic endocarditis with Aschoff-granuloma (six cases); (2) lymphocytic endocarditis (four cases); (3) endocardial thrombosis, and organization of such thrombi, including endocardial fibrous thickening (eight cases); (4) no pathologic findings in endocardium or myocardium (one case). Autopsies were obtained in four patients who died at varying times subsequent to the operation and the findings were completely in agreement with those at biopsy.

The authors conclude that rheumatic endocarditis can be present in spite of negative clinical findings and laboratory tests and, on the other hand pathologic sedimentation rate or antistreptolysin titers alone can not be regarded as positive evidence of activity. Therefore, if persisting rheumatic activity is to be regarded as an unfavorable condition for surgery, one positive test is not enough to advise against operations, but with two positive tests the patient must be carefully reconsidered before action is taken.

RINZLER

ROENTGENOLOGY

Larsson, H., and Palmlov, A.: Abdominal Aortography. Acta radiol. **38:** 111 (Aug.), 1952.

The authors discuss the toxic effects of abdominal aortography upon rabbits and in man. In rabbits the general toxicity of a 70 per cent concentration of the contrast medium is low, and the lethal dose much greater than that generally used in man.

Fifty-nine cases are reviewed with special reference to toxicity of the contrast substance. Renal studies including urea clearances, microscopic examinations and concentration tests show no significant change after the procedure.

The authors conclude that the complications are not due to the contrast substance but to the puncture itself.

SCHWEDEL

Bruwer, A., and Pugh, D. G.: A Neglected Roentgenologic Sign of Coarctation of the Aorta. Proc. Staff Meet., Mayo Clinic **27:** 377 (Sept.), 1952.

Rib notching is still the most important roentgenologic sign of coarctation of the aorta. In about a third of the cases of coarctation of the aorta in which operation was performed at the Mayo Clinic, another valuable sign was present on the posteroanterior roentgenogram. This consisted of a notch in the left border of the descending aorta just above the level of the left main pulmonary artery. This notch represents the coarctated segment. It may be present to a markedly varying degree, depending on a number of factors. In about 5 per cent of cases, the notch was the only definite roentgenographic sign of coarctation in the posteroanterior roentgenogram.

SIMON

OTHER SUBJECTS

Clark, R. J., Sprague, H. B., and Thorndike, A.: The Cardiac Work Classification Unit. New England J. Med. **247:** 290 (Aug. 21), 1952.

A work classification unit for cardiac patients has been established in the Bay State Medical Rehabilitation Clinic located within the grounds of the Massachusetts General Hospital. This clinic is intended to furnish a consulting service, to carry on research in the field of fitness for work and to further education of all those concerned with the utilization of workers with cardiac handicaps in industry. Referring agencies, private industry and insurance companies are expected to stand the cost of evaluation when possible although the Massachusetts Heart Association is underwriting the initial financial support. Careful evaluation of each patient by

a team of specialists is planned. No treatment will be outlined other than occupational therapy or informal psychotherapy.

ROSENBAUM

Stein, P.: Tendency toward Hypotension in Left Lateral Recumbency. Arch. Int. Med. **90:** 234 (Aug.), 1952.

The present report concerns the results of a study on 100 unselected persons in whom the influence of various positions upon the arterial blood pressure was observed. The statistical results reveal that the great majority had their lowest arterial blood pressure in the left lateral position. It is noteworthy that in certain persons a small difference in the degree of the body's rotation to the left side may significantly influence the level of the blood pressure.

Among the causative mechanisms which may bear some relation to the phenomenon of left lateral hypotension, a twist of the heart's pedicle at its entrance into the pericardium would be a factor if certain conditions prevail. Vasovagal reflexes of the type known to produce fall in blood pressure and shock would more readily occur in diseased and hypersensitive hearts. The resulting hypotension, reducing the coronary circulation significantly, would then explain the frequent appearance of anginal pain and dyspnea in patients with coronary disease whenever they rest on their left side. Other vagal reflexes will also have to be considered, especially reflexes produced by distention due to positional effects of an abdominal viscus, or by stimulation of the pressor-receptors in the aorta, pulmonary artery, and the carotid sinus. In addition, changes in the intrathoracic pressure, in the venous return, and in ventilatory and respiratory, as well as in neuroregulatory, factors and the element of vascular reactivity may play essential roles in creating a tendency to left lateral hypotension.

It appears that not one single causative factor, but rather a concatenation or combination of factors takes effect in the production of left lateral hypotension and its serious complications.

BERNSTEIN

Keys, A. Fidanza, F., Scardi, V., and Bergami, G.: The Trend of Serum-Cholesterol Levels with Age. Lancet **2:** 209 (Aug. 2), 1952.

Comparison is made (using identical technics) between age trends of serum cholesterol in men in Minnesota and those in a comparable group in Naples. Both groups showed a progressive rise to the age of 30 to 35 years. At that point a change in slope of the cholesterol-age curve occurred. The Minnesota men showed a more rapid increase in serum cholesterol thereafter. The Neapolitans showed no further increase in serum cholesterol after the age of 30 to 35 years. The authors believe this difference is related to differences in fat content of the habitual diets of the two groups and that it may account for the apparent lower incidence of coronary artery disease in Neapolitans of the socio-economic stratum studied.

MCKUSICK

Benjamin, J. E., and White, P. D.: Longevity with Complete Atrioventricular Block. J.A.M.A. **149:** 1549 (Aug. 23), 1952.

Two cases of complete atrioventricular block, lasting for 35 years or more, are reported. One patient, in her late fifties, died suddenly last year. Autopsy diagnosis was that of dilatation and hypertrophy of the heart, generalized arteriosclerosis, ascending aortic aneurysm of the arteriosclerotic type, diminutive left atrial appendage and a greatly enlarged right atrial appendage, a vestige of the left circumflex coronary artery, a 15 mm. area of calcification of the interatrial septum on the left side, and evidences of congestive failure. The other patient, at the age of 58, is living and well as of June, 1952. Both patients continued in very good health for more than 35 years, which illustrates the fact that complete atrioventricular block is compatible with long life and good health.

KITCHELL

Rantz, L. A., Di Caprio, J. M., and Randall, E.: Antistreptolysin O and Antihyaluronidase Titers in Health and in Various Diseases. Am. J. M. Sc. **224:** 194 (Aug.), 1952.

Antistreptolysin and antihyaluronidase are antibodies produced by the individual exposed to the enzymatic factors found in infections with hemolytic streptococci. The antibody titers reached their physiologic peaks in late childhood and then declined; however, the decrease of antihyaluronidase titer in the older groups was less than antistreptolysin. In rheumatic fever, the latter antibody was found to be elevated to 166 units per cubic centimeter or more in all cases, while the antihyaluronidase titers were inconsistent, although elevated in most instances. In acute glomerulonephritis, the findings were of the same order as in rheumatic fever. In addition, elevated titers of antistreptolysin were detected in some cases of rheumatoid arthritis, Henoch-Schonlein's purpura, erythema nodosum, and periarteritis nodosa. Exceedingly low titers were consistently encountered in cases of nephrotic syndrome. It is suggested that antibody titers of 500 units or more per cubic centimeter are indicative of recent streptococcal infection.

SHUMAN

Goggio, Alfred F.: Heart Disease in University Students. Ann. Int. Med. **37:** 155 (July), 1952.

Among 11,096 entering students at the University of California, 378 or 3.41 per cent were suspected to have heart disease on the basis of the history and/or physical examination. On the basis of a more detailed cardiovascular study, unquestion-

able heart disease was found in 0.38 per cent, of which 0.27 per cent had rheumatic heart disease and 0.11 per cent had congenital heart disease. There were, in addition, 0.23 per cent diagnosed as possible heart disease. The incidence of proved rheumatic heart disease was considerably lower among students born in California than in those born elsewhere. An incidence of rheumatic heart disease of only 0.12 per cent was found among those born within the state. Aortic insufficiency was found to be a relatively more frequent and important manifestation of rheumatic heart disease than is generally realized.

WENDKOS

Hardy, J. D., and Drabkin, D. L.: Measurement of Body Water. J.A.M.A. **149:** 1113 (July 19), 1952.

The several types of measurements that may be employed for the determination of total body water are outlined. Information derived from body water measurements in regard to body water and body fat, as well as body fluid compartments are discussed. The authors feel that deuterium oxide (heavy water) appears to be an excellent tracer substance for water and makes possible a more critical examination of rates of water turnover in the body and rates of transfer of water across various cell membranes. The authors feel the use of isotopes will extend knowledge of body fluid compartments and of water kinetics in the human body.

KITCHELL

Schneider, R. C.: Fat Embolism. A Problem in the Differential Diagnosis of Craniocerebral Trauma. J. Neurosurg. **9:** 1 (Jan.), 1952.

The occurrence of fat embolism to the cerebrum in patients with fractures of the long bones and possible head injury makes the differential diagnosis of the head lesion quite difficult. Three cases were observed in which the fat embolism secondary to long bone fracture simulated extradural hemorrhage, subdural hematoma, and midbrain injury respectively. (That fat embolism had occurred was demonstrated by the finding of fat droplets in the urine, eyeground changes, or necropsy.)

The diagnosis of this entity may rest upon: (1) a history of trauma to the long bones or to the adipose tissue, most often major fractures or crushing injuries; (2) increased pulse rate and fall in blood pressure; (3) increased respiratory rate, cough, and rales; (4) cerebral symptoms of diffuse nature and, perhaps, coma; (5) the finding of free fat droplets in the sputum; (6) the demonstration of free fat droplets in the urine; (7) evidence of fat in the circulating blood by funduscopic examination; (8) the finding of fat droplets in the venous blood; (9) the presence of petechial hemorrhages of the skin and conjunctiva occurring several days after the injury. In two of the cases here reported, the fat was found free in the urine, and in the third, it was found in the brain at necropsy.

There is some controversy as to the origin of the fat droplets. It has been felt that they arise from the fat in the marrow of the long bones and make their way to the brain via the circulation. It is not clear how they could pass the pulmonary capillary barrier unless there existed concomitant pulmonary damage. Some authors feel that the fat can traverse normal pulmonary capillaries; others postulate the presence of a patent foramen ovale. The role of vertebral veins has been emphasized by Batson as a route for cerebral metastases and emboli.

FROBESE

Master, A. M.: The Frequency of Functional Heart Disturbances. J.A.M.A. **150:** 195 (Sept. 20), 1952.

A study was made of 1000 consecutive private cardiac patients. Each had a physical examination, fluoroscopy, chest teleoroentgenogram, and a 12-lead electrocardiogram. If the 12-lead rest electrocardiogram was normal, the standard "two-step" exercise test was performed. If this was negative, the double "two-step" exercise electrocardiogram was taken. It was found that 618 patients suffered from organic heart disease and 382 from functional heart disturbances. The present report is made up of the group of 382 patients. It is suggested that heart conditions in patients who show no organic lesion should be termed "functional disturbance" rather than "functional disease." Of the 382 patients a ratio of three males to one female was noted. The majority were under 50 years of age. Pain or pressure in the chest was the most common symptom, and in general was very similar to such complaints encountered in organic heart disease. Fifty patients showed paroxysmal tachycardia, 18 showed premature beats. Neurocirculatory asthenia was noted in 48, anxiety neurosis in 13, hypertension in 17, and murmurs in 12. Chest pain was complained of in 42 per cent of the patients with paroxysmal tachycardia and 60 per cent of the patients with either neurocirculatory asthenia or anxiety neurosis. The hypertension found was usually very mild. The functional murmurs were all systolic in time and in no instance was a grade 3 murmur found. The author stresses that the frequency and magnitude of the problem of functional heart disturbances needs emphasis. The therapy of these cases is often unsuccessful but recognition of their frequent occurrence may lead to extensive research into the causes and to the discovery of methods for prophylaxis and treatment.

KITCHELL

De Soldati, L., Navarro Viola, R., and Mejia, R. H.: The Ballistocardiogram in Some Valvular Lesions and Congenital Malformations. Arch. mal. coeur **45:** 1016 (Nov.), 1952.

The authors describe and illustrate alterations of the ballistocardiogram found in certain types of rheumatic and congenital heart disease.

In mitral stenosis a diphasic H wave, a high L

wave and a deep M wave can usually be found. Aortic regurgitation, if present as isolated lesion, increases the amplitude of the J-K deflection but does not alter the ballistocardiogram if associated with mitral stenosis. In coarctation of the aorta the K wave is shortened and the I wave very deep. Both waves may become normal following surgical correction of the lesion. In a patent ductus arteriosus, a general enlargement of the amplitudes is found with augmentation of K and L deflections. The latter two large waves are also present in bicuspid aortic valves where the N wave is also large, but the over-all amplitudes not increased. No alterations were seen which would be typical for Lutembacher's syndrome.

PICK

Berner, J. H., Jr.: Orthostatic Hypotension in Diabetes Mellitus. Acta med. scandinav. **143:** 336, 1952.

A group of seven patients with severe diabetes mellitus and orthostatic hypotension is described. The ages ranged from 29 to 37 years with the exception of one patient aged 72 years. All had long-standing diabetes. Other abnormalities included retinopathy, nephropathy and neuropathy in nearly all of the group and abnormal bowel or bladder function in several of the patients. In these patients there was a distinct fall in both systolic and diastolic blood pressure on standing with no or only a slight increase in the pulse rate. The postural hypotension is attributed to damage to the autonomic nervous system.

ROSENBAUM

Turchetti, A., and Schiroza, G.: Essential Pulmonary Hypertension and its Phases of Evolution. Cardiologia **21:** 129 (Fasc. 3), 1952.

Following discussion of some divergent opinions concerning the pathogenesis of pulmonary vascular sclerosis and differences in terminology used for various cardiopulmonary syndromes the authors develop their own concept of primary pulmonary hypertension as etiologic factor. In the development of the disease three clinical stages may be observed.

As in the case of essential hypertension of the systemic circulation an initial, purely functional phase occurs in pulmonary hypertension. It is characterized by pressure elevation in the right ventricle and pulmonary artery—revealed by cardiac catheterization—in the absence of signs of right ventricular hypertrophy. The latter, in association with more or less pronounced sclerotic changes in the pulmonary arterial bed, is characteristic of the second "organic" stage of the disease. With further evolution and the onset of right ventricular failure the third, last, stage of the syndrome is reached in which some or all signs typical for chronic cor pulmonale may become obscured by the polymorphous symptomatology of heart failure in general.

The various phases of evolution are illustrated by two case histories. In the first instance the functional phase was observed in a 22 year old girl; in the other, a 57 year old woman, the development was followed over several years from the second organic phase to that of cardiopulmonary insufficiency.

PICK

Samuelsson, S.: Primary Cor Pulmonale. Chronic Cor Pulmonale Resulting from Pulmonary Hypertension of Unknown Etiology. Review of Literature. Report of 4 Cases. Acta med. scandinav. **142:** 177, 1952.

The author has selected 24 cases from approximately 120 which have been reported as instances of primary pulmonary vascular sclerosis. It is pointed out that in the remaining cases which are not accepted, there are many in which there is only minor pulmonary emphysema, pleuritis or inflammatory change in the pulmonary vessels. The diagnosis of primary cor pulmonale should be considered whenever a relatively young person develops dyspnea, cyanosis and edema, radiographic and electrocardiographic evidence of strain upon the right heart, and accentuation of the pulmonic second sound. Cyanosis is often relatively greater in degree than dyspnea and many of these patients are able to lie flat without discomfort. The prognosis is serious and in the 13 cases in which duration of symptoms is reported death occurred in four months to six years. Ordinary cardiac therapy is of little help and morphine is said to be absolutely contraindicated.

Four new cases are reported by the author. Symptoms had been 1 to 10 years prior to death. The electrocardiograms are said to show evidence of right heart strain in each case and in one patient right bundle branch block appeared in tracings made after exercise. Two of the patients received morphine by injection; one patient died after 24 hours without regaining consciousness and the other recovered only after vigorous oxygen and supportive treatment. Cardiac catheterization in one case disclosed a right ventricular pressure three times greater than normal and increased pressure in both pulmonary arteries. In two cases, microscopic examination disclosed some atheromatosis in the major pulmonary arterial branches, but the small branches of the pulmonary artery were normal. No microscopic examination was done in the third case and no autopsy was done on the fourth patient.

ROSENBAUM

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Publicaciones del Centro de Investigaciones Fisiologicas. Buenos Aires, University of Buenos Aires. 1951. 259 pages.

P-Q-R-S-T. A Guide to Electrocardiogram Interpretation. *Joseph E. F. Risemen, M.D. Clinical Associate of Medicine, Harvard Medical School; Instructor in Medicine, Tufts Medical School; Visiting Physician, Beth Israel Hospital, Boston, Mass.,* **ed. 3.** New York, Macmillan, 1952. 123 pages, 50 figures. $4.00.

The Principles and Methods of Physical Diagnosis. Correlation of Physical Signs with Physiologic and Pathologic Changes in Disease. *Simon S. Leopold, M.D., Associate Professor of Clinical Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania; Director of Teaching of Physical Diagnosis, School of Medicine; Chief of Thoracic Clinic, Hospital of the University of Pennsylvania.* Philadelphia, Saunders 1952. 430 pages, 390 illustrations with 19 color pages.

Lehrbuch der Inneren Medizin. 2. Verbesserte Auflage. *Edited by Helmut Dennig, Stuttgart; M. Broglic, Schlswig; H. Dennig, Stuttgart; K. Hansen und W. Gronemeyer, Lübeck; N. Henning, Wurzburg; A. Heymer, Essen; H. Reinwein, Kiel; F. Shellong, Münster; G. Schaltenbrand, Wurzburg; H. Schulten, Köln.* Stuttgart, Thieme, 1952. Vol. I, XVI. 972 pages, 243 figures. DM 41. Vol. II. XXIV. 1060 pages, 314 figures. DM 41.

The Unipolar Electrocardiogram. A Clinical Interpretation. *Joseph M. Barker, M.D. Cardiologist, Yater Clinic; Associate Professor of Clinical Medicine and Special Lecturer in Physiology, Georgetown University School of Medicine; Director, Heart Station and Visiting Physician, Georgetown University Hospital; Chief, Cardiology, Providence Hospital; Visiting Physician, Gallinger Municipal Hospital, Washington, D. C.; Consulting Cardiologist, Arlington Hospital, Arlington, Virginia. Assisted by Joseph J. Wallace and Advised by Wallace M. Yater. Foreword by Frank N. Wilson.* New York, Appleton-Century-Crofts, 1952. 655 pages, 457 figures.

Advances in Medicine and Surgery. From the Graduate School of Medicine of the University of Pennsylvania. *Editorial Committee: Julius H. Comroe, Jr., Chairman; David L. Drabkin, Oscar V. Batson, Aims C. McGuinness, Dean.* Philadelphia, Saunders, 1952. 441 pages, 43 figures, 18 tables.

Normal Blood Pressure and Hypertension. New Definitions. *Arthur M. Master, M.D., Charles I. Garfield, M.D., and Max B. Walters, M.D.,* Philadelphia, Lea & Febiger, 1952. 144 pages, 36 figures, 25 tables. $4.00.

Angiocardiographie et Cathétérisme Cardiaque. Etude critique de leur apport au diagnostic des Cardiopathies Congénitales. *Docteur Pol. Cahen, Chef de Clinique a la Faculte de Medecine de Lyon, France. Preface by Prof. Henri Hermann and Introduction by Prof. Ignacio Chavez.* Paris, G. Doin et Cie, 1952. 188 pages, 41 figures, 5 tables.

A Clinical Atlas of Blood Diseases, ed. 7. *A. Piney, M.D., M.R.C.P., Physician, St. Mary's Hospital, Plaistow, London.* Philadelphia, Blakiston, 1952. 136 pages, 47 figures, 45 figures in color. $5.00.

The Autonomic Nervous System. Anatomy, Physiology and Surgical Application, ed. 3. *James C. White, M.D., Massachusetts General Hospital, Boston; Reginald H. Smithwick, M.D., Boston; and Fiorindo A. Simeone, M.D., Cleveland.* New York, Macmillan, 1952. 569 pages, 108 figures, 39 tables. $12.00.

Cardiac Therapy. *Harold J. Stewart, M.D., Associate Professor of Medicine, Cornell University Medical College, New York; Attending Physician, New York Hospital; Head of Division of Cardiology, Department of Medicine New York Hospital, Cornell Medical Center.* New York, Paul B. Hoeber, 1952. 622 pages, 68 figures, 11 tables. $10.00

Il Cuore Artificiale (The Artificial Heart). *E. Tosatti.* Milan, Istituto Sierotera, 1951. 151 pages, 88 illustrations.

Atti della Societa Italiana di Cardiologia. XIII Congresso (1951). Folia Cardiologica, Vol. X, 1952.

Diabetic Glomerulosclerosis. The Specific Renal Disease of Diabetes Mellitus. *Harold Rifkin, M.D., Louis Leiter, M.D., Ph.D., and James Berkman, M.D.* Springfield, Ill., Charles C Thomas, 1952. American Lecture Series in Metabolism No. 130. 102 pages. 13 figures, 12 tables. $3.50.

Deformation and Flow in Biological Systems. *Edited by A. Frey-Wyssling, Professor of Plant Physiology, Swiss Federal Institute of Technology, Zurich.* Amsterdam, North-Holland Publishing Company, and New York, Interscience Publishers, 1952. 552 pages, 107 figures, 19 tables. $11.50.

Rheumatische Erkrankungen. Entstehung und Behandlung. *Professor Dr. Max Hochrein, Chefarzt der Medizinischen Klinik, Ludwigshafen/Rhein.* Stuttgart, Thieme, 1952. 416 pages, 121 figures. Ganzleinen DM36.

Acute Peripheral Arterial Occlusion. *William D.*

Holden, M.D., Oliver H. Payne Professor of Surgery, Western Reserve University, School of Medicine; Director of Surgery, University Hospitals of Cleveland, Cleveland, Ohio. Springfield, Ill., Charles C Thomas, 1952. American Lecture Series in Circulation No. 141. 66 pages, 2 figures.

Le Derivazioni Unipolari Nell'Elettrocardiografia Clinica. *Giovanni Gigli, University of Piza.* Pisa, Edizion, Omnia Medica, 1952. 260 pages, 148 figures. Prezzo L. 2.000.

Grundriss der Elektrokymographie. Phasenanalyse und Raumkymographie des Herzens. *Priv.-Doz. Dr. K. Heckmann, München.* Stuttgart, Thieme, 1952. 36 pages, 54 figures. Kart. DM 6.60.

Electrocardiography in Practice, ed. 3. *Ashton Graybiel, M.D., Captain, Medical Corps, U. S. Navy; Director of Research, U. S. Naval School of Aviation Medicine, Pensacola, Florida; Paul D. White, M.D., Executive Director, National Advisory Heart Council; Consultant in Medicine, Massachusetts General Hospital; Louise Wheeler, A.M., Executive Secretary, Cardiac Laboratory, Massachusetts General Hospital; and Conger Williams, M.D., Instructor in Medicine, Harvard Medical School; Associate Physician, Massachusetts General Hospital.* Philadelphia, Saunders, 1952. 378 pages, 294 figures. $10.00.

Cardiographic Technique. A Manual for Cardiological Technicians. *S. L. Barron, Member, Royal Institution of Great Britain; and A. Schott, M.D., (Heidelberg) M.R.C.S.; Medical Officer in charge of Cardiographic Department, Queen Mary's Hospital for the East End (London).* New York, Grune & Stratton, 1952. 166 pages, 59 figures. $4.50.

Die Angiographie zur Erkennung, Behandlung und Begutachtung peripherer Durchblutungsstörungen. *Dr. Med. Habil H. W. Pässler, Leverkusen.* Stuttgart, Thieme, 1952. 115 pages, 102 figures. Kart. DM 29.70.

Congenital Anomalies of the Heart and Great Vessels. *Maurice A. Schnitker, M.D., F.A.C.P., Lt. Col., U. S. Army, Medical Consultant, Pacific Theater, World War II; Director of Medicine, St. Vincent's Hospital; Senior Active Staff, Toledo Hospital and Maumee Valley Hospital; Consulting Staff, St. Luke's Hospitals and Toledo State Hospital.* New York, Oxford University Press, 1952. 306 pages, 19 figures, 12 tables. $8.00.

Blood Clotting and Allied Problems. Transactions of Fifth Conference, January 21 and 22, 1952, New York. *Edited by Joseph E. Flynn, M.D., Associate Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Sponsored by Josiah Macy, Jr., Foundation, New York.* Printed by Corlies, Macy and Company, Inc., New York, 1952. 368 pages, 148 figures, 25 tables. $4.95.

Congenital Heart Disease. The Clinico-Roentgenologic Picture after the Age of Two Years Based Upon about 200 Cases with Cardiac Catheterization. *Henning Gøtzche, Denmark.* Published by the author and printed by H. P. Hansens Bogtrykkeri, Copenhagen, Denmark, 1952. 254 pages, 49 figures, 53 tables. Danish Kroner 25.

Practical Blood Grouping Methods. A Manual of Immunohematology. *Robert L. Wall, M.D., Department of Research Medicine, The Ohio State University Hospital, Columbus, Ohio.* Springfield, Ill., Charles C Thomas, 1952. American Lecture Series in Hematology, No. 122. 175 pages. $5.00

Clinical Electrocardiography. A Textbook for Practitioners and Students. *Dr. Max Holzmann, Zurich. Translated by Douglas Robertson, M.A., D.M. (Oxon.), M.R.S.P. (London).* New York, London, Staples Press, 1952. 647 pages, 302 figures, 9 tables. $12.00.

Unipolar Lead Electrocardiography and Vectorcardiography. Including the Standard, the aV and V Leads, the Cardiac Arrhythmias and the Principles of Vectorcardiography, ed. 3. *Emanual Goldberger, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, New York; Cardiologist and Attending Physician, Lincoln Hospital, New York; Consulting Cardiologist, St. Joseph's Hospital, Yonkers, New York; Lecturer in Medicine, Columbia University, New York.* Philadelphia, Lea & Febiger, 1953. 601 pages, 312 figures. $10.00.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. 18. Tagung zu Bad Nauheim Vom 18. bis 20, April 1952. Hauptthema. Elektrokardiogramm. *Prof. Dr. Rudolf Thauer.* Darmstadt, Verlag Dr. Dietrich Steinkopff, 1952. 334 pages, 150 figures. DM 40.

Physiologic Therapy for Obstructive Vascular Disease. *Isaac Starr, M.D., Hartzell Research Professor of Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pa.* Modern Medical Monographs No. 6. New York, Grune & Stratton, 1953. 38 pages, 4 figures, 3 tables. $2.50.

Infectious Mononucleosis. *Sidney Leibowitz, M.D., Associate Physician, Beth Israel Hospital, New York.* Modern Medical Monographs No. 5. Grune & Stratton, Inc., New York, 1953. 163 pages, 3 figures, 15 tables. $4.75.

Pheochromocytoma and the General Practitioner. *Joseph L. DeCourcy, M.D., and Cornelius B. DeCourcy, M.D., DeCourcy Clinic, Cincinnati, Ohio.* Copyrighted 1952 by Barclay Newman. 165 pages.

1953 Medical Progress. A Review of Medical Advances during 1952. *Edited by Morris Fishbein, M.D.* New York, Blakiston, 1953. 301 pages, 5 tables. $5.00.

Éléments D'Électrocardiographie Théorique. *G. Duboucher.* Paris, Masson & Cie, 1952. 126 pages, 50 figures. 900 fr.

Bodily Physiology in Mental and Emotional Disorders. *Mark D. Altschule, M.D., Assistant Professor of Medicine, Harvard Medical School, Boston;*

Director, Internal Medicine and of Research in Clinical Physiology, McLean Hospital, Waverly; Visiting Physician, Beth Israel Hospital, Boston. New York, Grune & Stratton, 1953. 228 pages. $5.75.

Pathology of the Heart. *Edited by S. E. Gould, M.D., D.Sc., Clinical Professor of Pathology, Wayne University College of Medicine, Detroit; Pathologist, Wayne County General Hospital, Eloise; Consultant in Pathology, Veterans Administration Hospital, Dearborn, Mich.; Editor, American Journal of Clinical Pathology.* Springfield, Ill., Charles C Thomas, 1953. 1023 pages, 609 figures, 6 full color plates, 37 tables. $25.50.

AMERICAN HEART ASSOCIATION, INC.

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ASSOCIATION FELLOWSHIPS AND GRANTS

Applications for Research Fellowships and Established Investigatorships for the 1954–55 fiscal year must be received by Sept. 15, 1953. Applications for research grants-in-aid may be filed up to Dec. 1, 1953. Information and forms may be obtained from the Association's Medical Director.

Awards will be made from funds raised in the 1953 Heart Fund campaign by the American Heart Association and its affiliates throughout the nation.

RESEARCH GRANTS-IN-AID APPROVED

Eighty-nine grants-in-aid in the total amount of $473,930.59 for research studies have been approved by the Board of Directors upon recommendation of the Research Committee of the Scientific Council. The awards, which are for the 1953–54 fiscal year, are in addition to the Established Investigatorships and Research Fellowships announced in the May issue of CIRCULATION.

The awards follow:

Continued Grant Awards

Medical College of Georgia, Augusta, $4,462.50 for the study of the comparative effects of the adrenolytic agents on the cardiovascular system of the dog when administered in the presence of humoral or neurogenic hypertension, by *Raymond P. Alquist.*

Hahnemann Medical College and Hospital, Philadelphia, $5,250 for the investigation of the cardiovascular and respiratory dynamics in patients with valvular deformities before and after surgery, by *Charles P. Bailey.*

University of Pennsylvania Graduate School of Medicine, Philadelphia, $6,300 for the measurement of the work of breathing and pulmonary function in patients with dyspnea, by *Julius H. Comroe.*

American University of Beirut, Beirut, Lebanon, $4,725 for the effect of Krebs cycle inhibitors on the performance and metabolism of the isolated mammalian heart and the effect of cortical hormones on the salt and water excretion in a heart-lung-kidney preparation, by *George Fawaz.*

Mary Imogene Bassett Hospital, Cooperstown, N. Y., $7,140 for a correlation of the morphologic and metabolic aspects of cell damage, by *Joseph W. Ferrebee.*

Emory University School of Medicine, Atlanta, $5,250 for the study of the nature of the vascular response to sodium restriction, by *Eugene B. Ferris* and *Albert A. Brust.*

Georgetown University School of Medicine, Washington, D. C., $5,250 for hemodynamic studies in dogs using a variable heart pump permitting independent control of rate, output and ejection velocity, by *Edward D. Freis.*

Washington University School of Medicine, St. Louis, $5,250 for the study of metabolic factors in experimental heart failure, by *Robert F. Furchgott.*

University of Minnesota Medical School, Minneapolis, $6,825 for the investigation of etiologic and pathogenic mechanisms in rheumatic fever as revealed through studies of basic relationships of immunologic, endocrinologic, and biochemical events to pathologic processes related to those responsible for rheumatic disease, by *Robert A. Good.*

Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, $4,830 to study the nature of and the factors leading to the production of the vasoconstriction and the vasodilation which develops in perfused organs, by *Harold D. Green.*

University of Pennsylvania School of Medicine, Philadelphia, $10,500 for the study of the biochemical pathways by which cholesterol and fat are synthesized and metabolized in the body, the action of hormones upon the biosynthesis of cholesterol and lipids, by *Samuel Gurin.*

University of Utah College of Medicine, Salt Lake City, $5,250 for the study of adrenal hormones in the blood of patients with rheumatic fever and related conditions, by *Vincent C. Kelley.*

University of Tennessee College of Medicine, Memphis, $2,992.50 for the study of the role of ventricular filling in the production of the heart sounds with special attention to the etiology of the first and third sound, by *Robert C. Little.*

Washington University School of Medicine, St. Louis, $2,940 for the study of the isolation of specific heart proteins which bind cardiac drugs, by *Oliver H. Lowry.*

University of Pittsburgh School of Public Health, Pittsburgh, $8,925 for the study of congestive heart failure due to valvular disease upon myocardial metabolism in dogs, by *Robert E. Olson.*

Council on Rheumatic Fever and Congenital Heart Disease, $3,750 for cooperative research study of the relative effectiveness of ACTH and cortisone in the treatment of rheumatic fever and the prevention of rheumatic heart disease. *David D. Rutstein, Chairman.*

University of Wisconsin Medical School, Madison, $4,200 for the study of mechanism of pyruvate and α-ketoglutarate oxidation in heart muscle, by *D. Rao Sanadi.*

Harvard Medical School, Boston, $4,200 for studies on coronary heart disease, by *Monroe J. Schlesinger.*

Mount Sinai Hospital, New York, $3,150 for evaluation of the role of the kidney in the pathogenesis of heart failure, by *Jonas H. Sirota.*

Michael Reese Hospital, Chicago, $4,200 for the study of factors regulating renal function and electrolyte metabolism in experimental venous congestion with edema, by *Jeremiah Stamler.*

New England Center Hospital, Boston, $5,250 for the study of the relation of the endocrine system to the blood coagulation mechanism and to the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin and fibrinolytic substances in the treatment of thromboembolism, by *Mario Stefanini.*

Marine Biological Laboratory, Woods Hole, Mass., $10,000 for the study of the molecular mechanism of muscular contraction by *Albert Szent-Györgyi.*

University of North Carolina School of Medicine, Chapel Hill, $9,450 for an evaluation of the Macacus Rhesus monkey as an experimental animal for the production of atherosclerosis including studies on cholesterol metabolism using C^{14} labeled acetate, by *C. Bruce Taylor.*

Harvard Medical School, Boston, $4,200 for biochemical comparison of hypertensive and normal arteries, with particular attention to the electrolyte and intermediary metabolism, by *Louis Tobian, Jr.*

Harvard Medical School, Boston, $4,200 for studies on the relationship of the adrenal to hypertension, by *George W. Thorn.*

New Grant Awards

University of Cincinnati College of Medicine, Cincinnati, $3,150 for the study of the disappearance of veratrine during exposure to human red cells, by *George H. Acheson.*

University of Colorado School of Medicine, Denver, $4,252.50 for the study of immunophysiology, by *Jerry K. Aikawa.*

La Rabida Jackson Park Sanitarium, Chicago, $5,376 for the study of the nature and mode of action of the substance in testicular extract causing increased vascular permeability, by *Earl P. Benditt.*

Mary Imogene Bassett Hospital, Cooperstown, $5,250 for the study of lung volume restriction as a respiratory stimulus in normal subjects and patients with cardiorespiratory disease, by *James Bordley III.*

Instituto Nacional de Cardiologia, Mexico, $5,000 for the study of the heart deprived of the normal pacemaker with special regard to the relation of the sino-atrial node to the mechanism of atrial fibrillation, by *Joseph V. Brumlik.*

Fels Research Institute, Antioch College, Yellow Springs, Ohio, $7,728 for further studies with the dispersion oxygenator (artificial heart-lung), by *Leland C. Clark.*

Howe Laboratory of Ophthalmology, Harvard Medical School, Boston, $4,725 for the study of aging processes as reflected in the cornea, specifically the relation of fat deposition in the cornea to atheroma in the blood vessels, by *David G. Cogan.*

Temple University School of Medicine, Philadelphia, $4,725 for the preparation and study of angiotonase (hypertensinase), by *Dean A. Collins.*

State University of Iowa College of Medicine, Iowa City, $3,150 for the study of the effects of surgical and drug therapy on hepatic and renal circulation and function in certain cardiovascular disorders, by *James W. Culbertson.*

University of Pittsburgh School of Medicine

Pittsburgh, $6,195 for the study of cardiovascular effects of cation and anion depletion by vivodialysis, by *T. S. Danowski.*

Wayne University College of Medicine, Detroit, $4,935 for the isolation, chemical proof of structure and pharmacologic examination of the heart poison from Pilocereus Sargentianus Orcutt (Lophocereus schottii), by *Carl Djerassi.*

Hospital of the University of Pennsylvania, Philadelphia, $7,875 for the study of the urinary metabolites of C-21 cortical steroids determined by paper chromatographic methods, by *F. Curtis Dohan.*

University of Southern California School of Medicine, Los Angeles, $4,725 for the study of hereditary and environmental factors in hypertension, by *Douglas R. Drury.*

Faculty of Medicine, McGill University, Montreal, $6,819.75 for the study of chemical analyses of the aorta and tissue lipids during the earliest stages of the development of experimental atherosclerosis: their correlation with histochemical observations, by *G. Lyman Duff.*

Indiana University School of Medicine, Bloomington, $9,607.50 for the study of immunochemical and physical analysis of the time of appearance, distribution mechanism of synthesis and interaction of the contractile proteins, actin and myosin, in the morphogenesis of the heart, by *James D. Ebert.*

University of California Medical School, San Francisco, $7,708.05 for the study of distribution, penetration and rates of exchange of sodium, potassium and water in the gastro-intestinal tract, measured with Na^{24}, K^{42}, and D_2O, by *Isidore S. Edelman.*

Hospital of the University of Pennsylvania, Philadelphia, $4,058.25 for studies on the supraoptico-hypophyseal system in the normal dog pertaining to volume regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease, by *J. Russell Elkinton.*

State University Medical Center at Syracuse University School of Medicine, Syracuse, New York, $4,158 for the study of the influence of enzyme inhibitors and intermediary metabolites on cardiac function, by *Alfred E. Farah.*

University of Maryland School of Medicine, Baltimore, $5,680.50 for the study of factors causing obesity and the influence of obesity in the development of arteriosclerosis and other cardiovascular diseases, by *Frank H. J. Figge.*

Cardio-Pulmonary Laboratory, Bellevue Hospital, New York, $5,171.25 for the study of the role of the effective circulatory blood volume in congestive heart failure; the sensitivity of the respiratory center in cor pulmonale, by *Alfred P. Fishman.*

State University Medical Center at New York, New York, $3,150 for the study of the effect of lung expansion and of respiration upon the output of the right ventricle and upon pulmonary resistance, by *Noble O. Fowler.*

Harold Brunn Institute, Mount Zion Hospital, San Francisco, $3,150 for studies concerning the metabolism of cholesterol, by *Meyer Friedman.*

Johns Hopkins University School of Medicine, Baltimore, $5,250 for the analysis of factors responsible for experimental psychogenic tachycardia with especial attention to the role of Person in (1) producing changes in heart rate in the normal dog and (2) in the production of psychogenic tachycardia, by *W. Horsely Gantt.*

Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, $3,780 for the study of capillary circulation in experimental renal hypertension in dogs, by *Harry Goldblatt.*

Vanderbilt University School of Medicine, Nashville, $3,780 for the study of prolonged use of the oxygenator in experimental coronary occlusion, by *Frank Gollan.*

Yale University School of Medicine, New Haven, $6,048 for the study of hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes, by *Allan V. N. Goodyer.*

Northwestern University Medical School, Chicago, $4,200 for the study of the partition of coronary flow and the factors influencing it, by *Gerald R. Graham.*

University of California Medical School, Berkeley, California, $5,250 for tracer studies of the intermediate metabolism of amino acids and related compounds of significance for hypertension and arteriosclerosis, by *David M. Greenberg.*

University of Buffalo School of Medicine, Buffalo, $4,725 for hemodynamic studies in valvular heart disease, by *David G. Greene.*

Medical College of Georgia, Augusta, $8,400 for the training of candidates in cardiovascular research methods, by *W. F. Hamilton* and *R. P. Ahlquist.*

University of Utah College of Medicine, Salt Lake City, $6,300 for the study of pharmacology, physiology and biochemistry of the heart; research on the mechanism of action of digitalis, by *Stewart C. Harvey.*

Providence College, Providence, R. I., $2,003.68 for the study of labile digitonin precipitable metabolites of acetate in the chick embryo and living rat liver tissue, normal, regenerating and tumorous, by *Frederick C. Hickey.*

State University of Iowa College of Medicine, Iowa City, $5,250 for the study of cardiovascular adjustments to the sudden acute occlusion of the thoracic aorta and/or one or both of the vena cava, by *Steven M. Horvath.*

University of Tennessee College of Medicine, Memphis, $7,770 for the study of the role of the heart, blood vessels, liver and altered body fluids in the hypertension arising in dogs living a month or longer without kidneys, by *C. Riley Houck.*

Instituto de Biologia y Medicina Experimental, Buenos Aires, $10,000 for the study of experimental hypertension, by *Bernardo A. Houssay.*

Columbia University College of Physicians and Surgeons, New York, $4,200 for the study of cardio-

vascular problems as related to surgery, by *George H. Humphreys II.*

Montefiore Hospital, New York, $3,150 for the study of the surgical correction of mitral insufficiency, by *Elliot Hurwitt.*

University of Chicago School of Medicine, Chicago, $5,250 for the identification of the hypocholesteremic agent in a brain extract and studies on its mode of action, by *Richard J. Jones.*

St. Luke's Hospital, New York, $4,250 for the study of renal hemodynamics, albuminuria and electrolyte excretion, by *John H. Keating.*

University of South Dakota Medical School, Vermillion, $5,985 for biosynthesis and purification of high specific activity radiodigitoxin, by *F. E. Kelsey.*

Oklahoma Medical Research Institute, Oklahoma City, $5,433.75 for the study of the influence of adrenal cortical hormones on cardiac lesions and enzymes, by *Charles D. Kochakian.*

Harvard Medical School, Boston, $7,875 for the study of the circulatory action of the esters of protoverine and of germine, by *Otto Krayer.*

Harvard Medical School, Boston, $4,181.10 to study the partial synthesis of hypotensive veratrum alkaloids, by *S. Morris Kupchan.*

Massachusetts General Hospital, Boston, $4,961.25 for the study of factors that regulate extracellular fluid volume in the normal and edematous subject, by *Alexander Leaf.*

Montefiore Hospital, New York, $5,775; the use of a method of measuring lower extremity blood flow (muscle flow) to study the peripheral circulation and to measure certain aspects of muscle metabolism in normal subjects and cardiac patients, by *Louis Leiter.*

Peter Bent Brigham Hospital, Boston, $5,250, an investigation into the relation of renal failure to certain disorders of the cardiovascular system, by *John P. Merrill.*

Johns Hopkins Hospital, Baltimore, $5,499.11 for the study of factors governing the dye-dilution curve in the presence of cardiovascular shunts, by *William R. Milnor.*

The Middlesex Hospital, Medical School, London, England, $1,546.65, measurement of field potentials set up by the heart and other current-producing tissues, by *Clifford V. Nelson.*

New York University-Bellevue Medical Center, New York, $8,268.75 for the study of the temporary interruption of the cardiac and pulmonary circulations by hypothomia and with a new type of blood-oxygenator, by *John J. Osborn.*

University of California, College of Agriculture, Berkeley, $5,250 for the study of dietary factors influencing tissue levels of cholesterol with particular emphasis on the effect of plant sterols on the absorption and disposition of dietary cholesterol, by *Daniel W. Peterson.*

Research Institute, Montreal General Hospital, Montreal, $5,512.50 the influence of substituted acetic acids ($R \cdot CH_2COOH$) on fat metabolism in heart muscle, by *J. H. Quastel.*

Stanford University School of Medicine, San Francisco, $5,250 for the study of the effects of pulmonary hypertension on pulmonary gas exchange, by *Victor Richards.*

State University Medical Center at Syracuse University School of Medicine, Syracuse, New York, $5,250 for the study of the effects of cardiac glycosides and other substances on cardiac actomyosin threads, by *Jane Sands Robb.*

Cornell University Medical College, New York, $3,543.75 experimental studies on rheumatic fever, by *William C. Robbins.*

Harold Brunn Institute, Mount Zion Hospital, San Francisco, $3,150 for the study of the role of potassium in maintenance of blood pressure and peripheral vascular reactivity in normotensive and hypertensive states, by *Ray H. Rosenman.*

University of Washington School of Medicine, Seattle, $6,615 for the study of factors influencing diastolic filling and systolic emptying of the ventricular chambers, by *Robert F. Rushmer.*

Ohio State University College of Medicine, Columbus, $5,250 for the study of the changes in the ionic composition of the intracellular fluid in experimental and clinical hypertension, by *Leo A. Sapirstein.*

Washington University School of Medicine, St. Louis, Missouri, $3,932.25 for the study of experimental collagen disease. Functional and anatomic responses of the cardiovascular system in experimental animals to repeated antigenic assaults administered by various routes, by *John R. Smith.*

Cornell University Medical College, New York, $5,250 for the study of the distribution of electrolytes in acute renal failure, by *Roy C. Swan.*

Southwestern Medical School of the University of Texas, Dallas, $4,095, the use of ion exchange resins for quantitative analysis of biological material, by *John C. Vanatta.*

Heart Hospital, University of Minnesota, Minneapolis, $5,250 for studies in intermediary metabolism; the effect of alkali metal cations on acetate metabolism, by *Richard W. Von Korff.*

University of Illinois College of Medicine, Chicago, $5,250 for the study of the pathogenesis and treatment of experimental renal hypertension, spontaneous hypertension and neurogenic hypertension (dogs and monkeys), by *G. E. Wakerlin.*

Duke University School of Medicine, Durham, $5,250 for the study of the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation, by *James V. Warren.*

New York University College of Dentistry, New York, $4,620 for the study of the relation of platelet function to blood coagulation, with particular reference to platelet morphology, release of vasoconstrictor substance from the platelets and the formation of hemostatic platelet plugs in rats with coagulation disorders, by *Marjorie B. Zucker.*

ANNUAL ELECTIONS

Robert L. King, M.D., Seattle, assumed the Presidency of the Association for the 1953–54 term at the Twenty-Ninth Annual Meeting in Atlantic City in April. Dr. King is a partner in the Mason Clinic in Seattle and is Chief of Medical Service and Secretary of the Board of Trustees of Virginia Mason Hospital in that city. He is also Clinical Associate Professor of Medicine at the University of Washington School of Medicine, and Consultant in Cardiology to the Department of Health, Territory of Alaska. A member of the Board of Directors of the American Heart Association since 1948, Dr. King had been a Vice-President since 1951. He succeeded Dr. Irving S. Wright, New York, who, as retiring President, became Chairman of the Association's Scientific Council.

E. Cowles Andrus, M.D., Associate Professor of Medicine at Johns Hopkins University Medical School, Baltimore, was chosen President-Elect. He has been a Vice-President of the Association and a member of the Executive Committee of the Board of Directors for several years.

Elected as Vice-Presidents were A. W. Robertson, Pittsburgh, and Robert W. Wilkins, M.D., Boston. Vice-Presidents re-elected were Mrs. Alben W. Barkley, Paducah, Ky.; Bruce Barton, New York; T. Duckett Jones, M.D., New York; Frederick K. Trask, Jr., New York; Irvine H. Page, M.D., Cleveland; and John J. Sampson, M.D., San Francisco. Berkeley D. Johnson, New York, was re-elected Treasurer.

Bruce Barton Named Board Chairman

Bruce Barton, New York, has been named Chairman of the Board of Directors of the Association. He succeeds A. W. Robertson, Pittsburgh, who is now a Vice-President of the Association. Mr. Barton is Chairman of the Board of Batten, Barton, Durstine and Osborn, advertising agency, and served as National Chairman of the Heart Fund campaign during the past three years.

Board Members

New members elected to the Board of Directors (for a three-year term except where otherwise indicated) were: Emmet B. Bay, M.D., Chicago; Lewis T. Bullock, M.D., Los Angeles (vacancy, one year); S. DeWitt Clough, Chicago; Mrs. Preston Davie, New York; Thomas J. Deegan, Jr., New York; Thomas M. Durant, M.D., Philadelphia; Edgar Durbin, M.D., Denver; Frank N. Isbey, Detroit; Louis N. Katz, M.D., Chicago (vacancy, two years); Jerome G. Kaufman, M.D., Newark; Edwin P. Maynard, Jr., M.D., New York; Homer P. Rush, M.D., Portland, Ore.; David D. Rutstein, M.D., Boston; Carter Smith, M.D., Atlanta (vacancy, two years); Sylvester L. Weaver, Jr., New York.

Scientific Council Board Members

Chosen to represent the Scientific Council and its component sections and councils on the Board of Directors were the following:

Representing the Scientific Council as a whole: Stanley E. Bradley, M.D., New York; Francis L. Chamberlain, M.D., San Francisco; Eugene A. Stead, Jr., M.D., Durham, N. C.; Irving S. Wright, M.D., New York.

Representing the Council on Rheumatic Fever and Congenital Heart Disease: John P. Hubbard, M.D., Philadelphia; George M. Wheatley, M.D., New York.

Representing the Council for High Blood Pressure Research: Adrian D. Joyce, Cleveland; Frank E. Joseph, Cleveland.

Representing the Section on Circulation: Nelson W. Barker, M.D., Rochester, Minn.; George E. Burch, M.D., New Orleans.

Representing the Section on Clinical Cardiology: A. Carlton Ernstene, M.D., Cleveland; Hugh Morgan, M.D., Nashville, Tenn.

Officers of Scientific Council and Its Sections

In addition to Irving S. Wright, M.D., New York, who, as retiring President of the Association, became Chairman, George E. Wakerlin, M.D., Chicago, has been named Vice-Chairman of the Scientific Council. A. Carlton Ernstene, M.D., Cleveland, has been chosen Secretary.

The following have been named officers of the constituent Sections and Councils of the Scientific Council:

Council on Rheumatic Fever and Congenital Heart Disease: J. G. Fred Hiss, M.D., Syracuse, N. Y., Chairman; Katherine D. Brownell, M.D., New York, Vice-Chairman.

Section on Circulation: George E. Burch,

M.D., New Orleans, Chairman; A. Wilbur Duryee, M.D., New York, Vice-Chairman; Grace M. Roth, Ph.D., Rochester, Minn., Secretary.

Council for High Blood Pressure Research: Adrian D. Joyce, Cleveland, President. Mr. Joyce, Chairman of the Board of the Glidden Company, succeeded the late Alva Bradley, who died of a heart ailment last March. Frank E. Joseph, Cleveland, was named Vice-President, and George E. Merrifield, Cleveland, was chosen Secretary. George E. Wakerlin, M.D., Chicago, was named Chairman of the Medical Advisory Board. Eugene B. Ferris, M.D., Atlanta, was named Vice-Chairman.

Section on Clinical Cardiology: A. Carlton Ernstene, M.D., Cleveland, Chairman; Emmet B. Bay, M.D., Chicago, Vice-Chairman; Carter Smith, M.D., Atlanta, Secretary.

Section on Cardiovascular Surgery: George H. Humphreys II, M.D., New York, Chairman; Robert E. Gross, M.D., Boston, Vice-Chairman; Jere W. Lord, Jr., M.D., New York, Secretary.

Section on Basic Science: William F. Hamilton, Ph.D., Augusta, Ga., Chairman; Louis N. Katz, M.D., Chicago, Vice-Chairman; Hyman S. Mayerson, Ph.D., New Orleans, Secretary.

GOLD HEART AWARDS

The American Heart Association's Gold Heart Awards for outstanding contributions to cardiovascular medicine and the Heart Program were presented at the Annual Dinner in Atlantic City in April to Haven Emerson, M.D., and Bruce Barton, both of New York City. Dr. Emerson, a founder of the American and New York Heart Associations, was honored for his creative leadership in the broad field of public health for nearly half a century. Dr. Emerson, who began the practice of medicine in 1899, is now retired from his many academic and public positions. Mr. Barton, noted advertising executive and author, was honored for his service as National Chairman of the 1951, 1952 and 1953 Heart Fund campaigns, and as a Vice-President of the Association.

MEDALLION TO DR. WRIGHT

The Association's Distinguished Service Silver Medallion was presented to Irving S. Wright, M.D., as retiring President, at the Annual Dinner. Dr. Wright, Professor of Clinical Medicine, Cornell University Medical College, is a Past President of the New York Heart Association and a member of its Board of Directors since 1935.

FIRST BLAKESLEE AWARD FOR SCIENTIFIC REPORTING

The Association's first annual $1,000 Howard W. Blakeslee Award for outstanding scientific reporting in the cardiovascular field was presented to Wade Arnold, Executive Producer of the National Broadcasting Company, at the Annual Dinner. The Award was established in memory of Howard W. Blakeslee, late science editor of the Associated Press. Mr. Arnold received the award for his "creative achievement in writing and producing the documentary radio program, 'Only One to a Customer.' "

MEETING OF COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

Papers by five research investigators were read at the Scientific Sessions held in conjunction with the Annual Meeting of the Council for High Blood Pressure Research, which took place in Cleveland in May. The investigators and the titles of their papers were as follows:

R. W. Sevy, Ph.D., University of Illinois College of Medicine, Chicago: "The Anterior Pituitary and Adrenal Cortex in Experimental Hypertension";

George M. C. Masson, M.D., Cleveland Clinic, Cleveland: "The Role of Renin in Experimental Hypertensive Vascular Diseases";

Simon Rodbard, Ph.D., M.D., Michael Reese Hospital, Chicago: "Salt-Water Balance and Blood Pressure";

D. M. Green, M.D., University of Southern California Department of Medicine, Los Angeles: "Changing Patterns of Sodium Metabolism in Hypertension";

George A. Perera, M.D., College of Physicians and Surgeons, Columbia University, New York: "Electrolyte Participation in Human Hypertension."

The proceedings of this Council meeting will be published at a later date. The proceedings of the 1952 Annual Council Meeting, published by the Association in a paper-covered monograph, are currently available at $1.75 per copy. The volume includes six scientific papers summarizing recent developments in research

and treatment in the cardiovascular field, and a number of informal addresses to laymen by physicians prominent in the activities of the Association.

CARDIOLOGY CONGRESS

L. Whittington Gorham, M.D., New York, has been named Secretary-General of the Second International Congress of Cardiology. The Congress will take place in Washington, D.C., Sept. 12 through 15, 1954. Dr. Gorham is Director of the Public Health Research Institute of the City of New York and Chairman of the New York State Public Health Council.

The 1954 Scientific Sessions of the American Heart Association, which are usually held in conjunction with the Association's Annual Meeting, will be held instead on September 16–18, in Washington, immediately following the International Congress of Cardiology.

1954 ANNUAL MEETING

The 1954 Annual Meeting of the Association will take place in Chicago on Thursday and Friday, April 1 and 2, at the Conrad Hilton Hotel. It will be followed by special Scientific Sessions, conducted by the Section on Clinical Cardiology of the Scientific Council, on Saturday and Sunday, April 3 and 4. These sessions will precede the annual meeting of the American College of Physicians.

"NOMENCLATURE AND CRITERIA"

A completely revised and greatly expanded edition of the standard medical handbook, *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*, has been prepared by the New York Heart Association and is now being distributed by the American Heart Association and its affiliates. The illustrated handbook is intended primarily to clarify and standardize the language used by the medical profession in diagnosing cardiovascular diseases. By enabling physicians to record their findings with precision, it assists them in communicating vital information to other physicians or to hospital or clinic personnel who cooperate in the management of the patient.

Nomenclature and Criteria was first published in 1929. This, the fifth edition, was prepared by the Criteria Committee of the New York Heart Association, under the Chairmanship of Harold E. B. Pardee, M.D., as were the preceding four. The fourth edition was issued in 1939.

Some entirely new concepts and viewpoints in the cardiovascular fields, developed over the past ten years, are presented in the new edition. For the first time it includes a section on diseases of the peripheral vessels. Extensive revisions have been made and new material added to the sections on x-ray and electrocardiography to conform with recent advances. The criteria for the diagnosis of rheumatic fever have been amplified and made more exacting, and the criteria for diagnosis of congenital anomalies have been expanded.

The new edition also contains a revised Chart of Functional Capacity and Therapeutic Classification to help the physician prescribe the amount of physical activity appropriate to a patient. Developed by the Criteria Committee of the New York Heart Association, this chart is generally accepted as standard throughout the United States. For the convenience of doctors and other professional persons, the American Heart Association has reprinted the chart on a handy 4 by 9½ inch card to be kept for quick reference in a desk corner or jacket pocket, or for use as a book mark. Among other advantages, the classification chart offers a uniform terminology for transmitting information needed by the employment counselor or rehabilitation worker.

Nomenclature and Criteria may be purchased through heart associations or book stores at $4.95 a copy.

FILMS ON CARDIOVASCULAR DISEASE

A volume reviewing 62 available films and listing 118 additional films in the cardiovascular field has recently been published as a joint undertaking of the American Heart Association and the Association of American Medical Colleges. Entitled *Films in the Cardiovascular Diseases: Survey, Analysis, and Conclusions*, the book was prepared by David S. Ruhe, M.D., New York, and his associates of the Medical Audio-Visual Institute of the Association of American Medical Colleges, assisted by panels of cardiologists. It is directed to those who are

interested in or find a need to utilize films in the teaching of cardiovascular subjects. The price of the book is $1.50 paper-bound, $2.00 cloth-bound.

TRAINING COURSE FOR CARDIOVASCULAR INVESTIGATORS

A training course for cardiovascular investigators is being offered by the Departments of Physiology and Pharmacology, Medical College of Georgia. This 12-month training program in the disciplines of cardiovascular research, for a limited number of qualified individuals, is supported by the National Heart Institute, U. S. Public Health Service. The American Heart Association also is contributing $8,400 toward the course for the first year. The course begins July, 1953. W. F. Hamilton, Ph.D. and R. P. Ahlquist, Ph.D., will be in charge.

To accelerate the development of available qualified personnel for research in cardiovascular problems, the year's course includes the following: formalized technical training in various research methods employed on humans and animals; assistance of qualified investigators in basic animal research (Professors Philip Dow and John Remington and Associate Professor Robert Alexander will head such research groups). Supervised experience in independent research and manuscript preparation will conclude the training program.

Graduates in medicine or related sciences who are highly recommended and acceptable to the Program Directors are eligible. There are no tuition fees. The research traineeships carry an annual stipend of $3400, plus an allowance of $350 for each dependent. First-class transportation will be furnished a research trainee (but not his dependents) from his home or institution of residence to Augusta, Ga. Return transportation is not provided.

For queries or application forms write: W. F. Hamilton, Ph.D., Department of Physiology, or R. P. Ahlquist, Ph.D., Department of Pharmacology, Medical College of Georgia, Augusta, Ga.

ELECTROCARDIOGRAPHIC INTERPRETATION

A course in Electrocardiographic Interpretation for graduate physicians will be given at the Michael Reese Hospital by Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, and associates. The class will meet daily from 9:00 a.m. to 5:00 p.m., August 3 through August 15.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

INSTITUTE ON RHEUMATIC FEVER

La Rabida Sanitarium, Chicago, anounces the inauguration of an annual institute in the field of rheumatic fever. The five-day sessions will begin Oct. 12, 1953.

For four days the institute will be conducted by members of the hospital staff, together with others selected from medical schools in Chicago with which the hospital is affiliated, and by several invited guests. It will be directed primarily to the general practitioner or family physician and to nurses, medical social workers, occupational therapists, dentists and others with a similar interest in the subject. There will also be a scientific session.

Sessions will be provided also for the public, especially patients and their parents. Advance registration will be required for those who wish to attend the entire institute. Visitors to individual sessions will be admitted by card on previous application. There will be no admission or tuition charge. For further information, apply to Institute, La Rabida Sanitarium, East 65th St. and South Shore Drive, Chicago 49.

SYMPOSIUM

The University of Vermont, in conjunction with the Vermont and New Hampshire Heart Associations, will hold an International Symposium on "Cardiovascular Regulations" in Burlington, Vt., Sept. 8 through 10. Participants from abroad will include workers in the field from Europe, South America and Africa. Present plans call for formal communications to be presented by guests from abroad with American participants joining in the discussion. Additional information may be obtained from Wilhelm Raab, M.D., University of Vermont College of Medicine, Burlington.

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 172.

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